Medicaid Dossier for *Avodart*

This information is provided in response to your request for information about Avodart® (dutasteride).

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In order for GlaxoSmithKline to monitor the safety of our products, we encourage healthcare professionals to report adverse events or suspected overdoses to the company at 888-825-5249. Please consult the attached Prescribing Information.

This response was developed according to the principles of evidence-based medicine and, therefore, references may not be all-inclusive.

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1. Change Summary

In June 2008, *Avodart* received the indication for use in combination with the alpha blocker, tamsulosin.

2. EXECUTIVE SUMMARY

Background Information

Benign prostatic hyperplasia (BPH) or enlarged prostate is the fourth most prevalent disease in men 50 years of age and older.[1] Half of men over the age of 50 and 90% over the age of 80 will be affected by this disease.[2] BPH is a progressive disease that can lead to serious consequences.[3,4] Current goals of BPH therapy include identifying patients at risk through appropriate diagnosis, improving American Urological Association Symptom Index (AUA-SI) scores, decreasing the risk of acute urinary retention (AUR) and BPH-related surgeries, and slowing progression of the disease.[5] This leads to reduced urinary symptoms and improved quality of life. *Avodart* (dutasteride) is a dual 5α-reducatase inhibitor (5ARI) indicated for the treatment of symptomatic BPH in men with an enlarged prostate to improve symptoms, reduce the risk of AUR, and reduce the risk of the need for BPH-related surgery.[6] *Avodart* is also indicated for the treatment of symptomatic BPH in men with an enlarged prostate when used in combination with the alpha-blocker, tamsulosin. *Avodart* acts by inhibiting type 1 and type 2 5α-reductase, which suppresses dihydrotestosterone (DHT) levels and therefore, reduces the size of the prostate and modifies disease progression.

Clinical Data from Monotherapy trials

The efficacy and safety of *Avodart* have been evaluated in patients with BPH in three identical two year double-blind, placebo-controlled clinical trials.[7] Over 4,300 men with BPH were randomly assigned to receive *Avodart* 0.5 mg daily or placebo in these trials. The subsequent two years consisted of an open-label design in which all patients received *Avodart* 0.5 mg daily.[8] A total of 2,167 patients received *Avodart* and 2,158 received placebo for the 2-year double-blind phase of the trial. During the 2-year extension phase, 1,188 patients continued *Avodart* and 1,152 patients initiated *Avodart*. A total of 1,667 patients completed the 4-year study.

Monotherapy trials have demonstrated clinical benefits in patients treated with *Avodart* 0.5 mg daily compared to placebo at 24 months.[7] The primary efficacy endpoint in these three large double-blind, placebo-controlled clinical trials was the incidence of acute urinary retention and BPH-related surgery.

- 57% reduction in the risk of AUR compared with placebo ($P < 0.001$)
- 48% reduction in the risk of BPH-related surgical intervention compared with placebo ($P < 0.001$)

Therapy with *Avodart* was also associated with improvements in a number of secondary endpoints.

- Improvement in symptoms, as measured by the AUA-SI score, with mean decrease from baseline of -4.5 units for *Avodart* versus -1.7 units for placebo ($P < 0.001$). Of note, the AUA Guidelines state that a change of 3 units is perceivable improvement in urinary symptoms to patients.[9]
- Reductions in mean prostate volume (PV) of –25.7% (adjusted for placebo)
- Significant decrease in transition zone volume of - 24.3% ($P < 0.001$)
- Significant increase in urinary flow rate (Qmax) of 2.2 mL/sec ($P < 0.001$)
- Prostate specific antigen (PSA) decreases by about half by month 6 and is maintained for a total of 24 months, allowing it to be a reliable diagnostic measurement
- Median reduction from baseline in DHT concentration of 93.7%

The primary and secondary endpoints improved or were maintained in the subsequent 2-year open-label extensions of these trials for a total of 4 years.[8] *Avodart* provides long-term symptom improvement, as measured by a decrease in AUA-SI of 6.5 units and increase in Qmax of 2.7 mL/sec over 4 years in patients who continued *Avodart*. In addition, *Avodart* modifies disease progression by reducing mean prostate volume by 27.3% at 4 years.

Clinical Data from Combination Therapy Trial

The efficacy of combination therapy (*Avodart* 0.5 mg daily plus tamsulosin 0.4 mg daily, n = 1,610) was compared with *Avodart* alone (n = 1,623) or tamsulosin alone (n = 1,611) in a 4-year international multicenter, randomized, double-blind study.[6,10] A 2-year interim analysis was performed. Once the analysis of the 4-year data is complete, these results will be published.

Most of the 4,844 subjects randomly assigned to receive combination, *Avodart*, or tamsulosin completed 2 years of double-blind treatment (79%, 80%, and 78%, respectively). The primary efficacy endpoint evaluated during the first 2 years of treatment was change in international prostate symptom score (IPSS). Combination therapy was statistically superior to each of the monotherapy treatments in decreasing symptom score at Month 24. This difference was seen by Month 9 and continued through Month 24.

- Mean change from baseline in IPSS symptom scores was -6.2 for combination, -4.9 for *Avodart,* and -4.3 for tamsulosin

Therapy with *Avodart* was also associated with improvements in several secondary endpoints at 24 months. Combination therapy was statistically superior to each of the monotherapy treatments in increasing Qmax at Month 24. This difference was seen by Month 6 and continued through Month 24.

- Mean increase from baseline in Qmax was 2.4 mL/sec for combination, 1.9 mL/sec for *Avodart*, and 0.9 mL/sec for tamsulosin
- Mean percent change from baseline in prostate volume was -26.9% for combination therapy, -28.0% for *Avodart*, and 0% for tamsulosin
- Mean percent change from baseline in transition zone volume was -23.4% for combination therapy, -22.8% for *Avodart* and +8.8% for tamsulosin

Quality of Life

BPH is primarily a quality of life disease and the consequences of the urinary symptoms can affect physical, social, and psychological well being.[11] BPH can also significantly impact functional health by interfering with activities of daily living. The degree to which BPH symptoms affect quality of life and functional health is important to assess, since these factors may directly impact a patient's motivation to seek treatment. The BPH Impact Index (BII) is a four-item assessment tool that evaluates the extent to which symptoms affect the patient's health status.[12] It measures physical discomfort, activity restriction, bother and worry associated with lower urinary tract symptoms. A decrease in BII of -0.5 correlates with patient perception of improvement and thus, correlates with a clinically significant difference. *Avodart* significantly improved patient health status compared with placebo ($P < 0.001$) as measured by reductions in the BII beginning at Month 12 in two studies ($P < 0.001$) and beginning at Month 6 in the third study ($P = 0.014$).[13,14,15] For all three studies, these improvements were sustained through Month 24.

Safety

During the double-blind phase of the monotherapy trials, adverse events were reported in a similar proportion of patients treated with *Avodart* (77%) or placebo (75%).[6,7] Most adverse events were mild or moderate in intensity and generally resolved while on treatment with *Avodart* and placebo. The drug-related adverse events reported in the clinical trials included impotence, ejaculation disorders, decreased libido and gynecomastia. The most common adverse events leading to withdrawal in both treatment groups were associated with the reproductive system. The overall incidence of drug-related adverse events during the open-label phase was 12% in the placebo/*Avodart* group (P/A) and 8% in the *Avodart*/*Avodart* group (A/A), mostly due to drug-related sexual adverse events (9% in the P/A group and 5% in the A/A group).

In the 2 year interim analysis of the CombAT trial, the overall incidence of adverse events and serious adverse events were similar across the treatment groups.[10] The most common drug-related adverse events in patients receiving combination therapy were impotence, decreased libido, breast disorders, ejaculation disorders, and dizziness.[6,10] The incidence of drug-related adverse events was significantly higher in the combination therapy group compared with each monotherapy group. The discontinuation rate due to drug-related adverse events was 5% for combination therapy and 3% for *Avodart* and tamsulosin as monotherapy.

Summary

In summary, *Avodart* reduces urinary symptoms, reduces the size of the prostate and reduces the risk of AUR and BPH-related surgery.[6] *Avodart* 0.5 mg Soft Gelatin Capsules taken once daily alone or in combination with the alpha-blocker, tamsulosin are proven to be safe and tolerable in treating symptomatic BPH in men with an enlarged prostate.

3. DISEASE DESCRIPTION

3.1 Epidemiology of Benign Prostatic Hyperplasia

DESCRIPTION AND FUNCTION OF THE PROSTATE

The prostate gland is a walnut shaped organ that lies at the base of the bladder in men. The size (volume) of the prostate is usually expressed in cubic centimeters (cc). The normal prostate is about 20cc and weighs less than an ounce. The gland is soft and rubbery in consistency.

The prostate serves as an accessory reproductive organ, producing a thin, milky fluid that helps sustain sperm cells following ejaculation. The prostate contributes 1.5 to 2 mL toward the total average ejaculate volume of about 3 mL. The fluid is alkaline, which enhances the viability of sperm cells in the acidic environment of the vagina. Prostatic fluid also contains a protein called prostate-specific antigen (PSA) that helps liquefy semen after ejaculation and coagulation.[16,17]

EPIDEMIOLOGY OF BENIGN PROSTATIC HYPERPLASIA

Benign prostatic hyperplasia (BPH) is a non-malignant enlargement of the prostate. Although the prostate continues to grow during most of a man's life, the enlargement does not usually cause problems until later in life and is found to occur predominantly in men over the age of 60 years.[18] The estimated lifetime risk of requiring treatment for BPH in a 50 year-old man is 40%.[19] Prevalence increases with each decade of life. Fifty percent of men over the age of 50 and 90% of men over the age of 80 are affected with BPH.[2] Approximately 50% of men with enlarged prostates will require medical intervention and treatment.[20]

Benign prostatic hyperplasia is a progressive disease. As the enlarged prostate continues to increase in size, the risk of acute urinary retention (AUR) and BPH-related surgery increases. A 60-year old man with a 20-year life expectancy has a 23% risk of developing AUR.[21] Among men 50 years of age, the lifetime incidence of surgical or medical intervention due to BPH is estimated at 35%.[22]

BPH often presents as lower urinary tract symptoms (LUTS). LUTS is mainly characterized by voiding symptoms, especially hesitancy, decreased urinary flow rate, and prolonged time to empty the bladder. About 15% to 25% of men have LUTS that are considered moderate to severe.[23] In one retrospective, cohort study consisting of 80,774 males aged 45 or older, the overall incidence rate of LUTS/BPH was 15 per 1000 man-years, which increased linearly with age. LUTS incidence increased in a linear fashion as a function of age.[24]

Mortality and Morbidity

The mortality rate attributable to BPH has declined considerably over the last 30 years due to improvements in surgical care and medical management during the post-operative period. The decline; however, has been primarily in countries where mortality rates are now 0.3 to 3 per 100,000 patients. Benign prostatic hyperplasia mortality remains higher (about 4 to 8 per 100,000 patients) in Central America and Eastern Europe.[25]

Morbidities associated with BPH vary according to lower urinary tract symptoms (LUTS), bladder outlet obstruction (BOO), and benign prostatic enlargement (BPE) measures used for assessment. Patients can develop BPH complications that require surgery such as AUR, recurrent urinary tract infections, gross hematuria, bladder stones, renal insufficiency due to BPH, renal failure due to obstruction, and large bladder diverticulitum.

Acute urinary retention is an undesirable event that frequently occurs in the natural history of BPH. It is a painful condition requiring immediate medical treatment and frequently surgical intervention.[23,26] Over time, chronic retention could develop, characterized by a painful, palpable bladder. Some complications of AUR include frequent but incomplete urination, nocturia, urgency, and urge incontinence. More severe cases may involve renal impairment, hypertension, and hydronephrosis (high-pressure chronic retention). Management with catheterization may lead to excessive diuresis with consequent electrolyte imbalance.[23] It has been estimated that AUR is the indication for surgery in 25% to 30% of patients undergoing transurethral radical prostatectomy (TURP).[26,27,28] Data from a population-based study of male residents in US-based Olmsted County suggest that the probability of a 60 year-old man experiencing AUR in the subsequent 20 years is substantial, approximately 23%.[21,26,29] Results from the Olmsted County Study also indicated that LUTS, depressed peak urinary flow rates, enlarged prostates and older age are associated

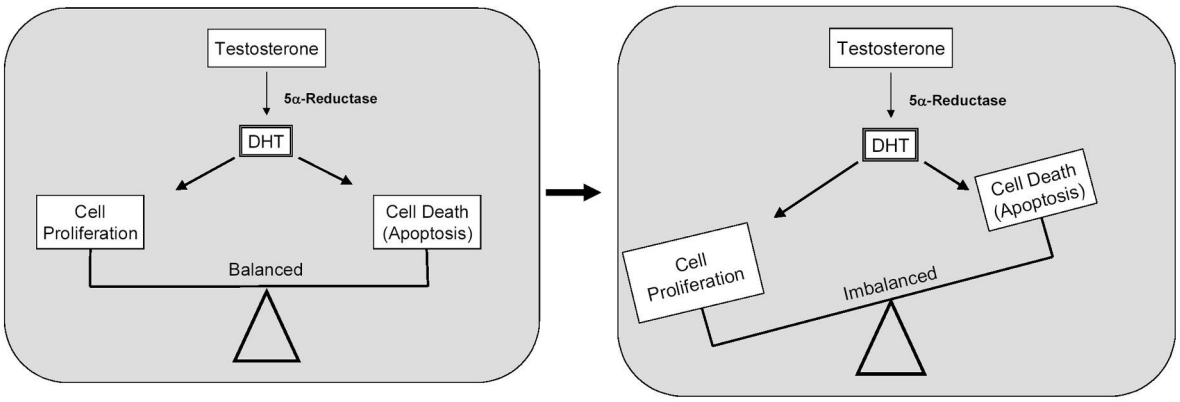
with an increased risk of AUR. In addition, men with prostate volumes ≥30 mL were three times more likely to develop AUR than men with smaller prostate volumes. Men with prostate specific antigen (PSA) levels >1.4 ng/mL were three times more likely to develop AUR than men with lower PSA values.[21,30]

3.2 Pathophysiology for Benign Prostatic Hyperplasia

The symptoms of BPH result from the pressure exerted by an enlarged prostate on the urethra and the gradual obstruction of urine flow.[31] The etiology of benign prostatic enlargement is a multifaceted pathophysiologic process involving hormone balance, aging, genetic factors, and environmental factors; however, it is essentially an androgen-dependent process, since androgens, specifically dihydrotestosterone (DHT), must be present for the disease to develop and progress.[31,32]

Histologic evidence of BPH first develops in the periurethral transition zone of the prostate,[33] where increased numbers of cells may be the result of increased cellular proliferation, a failure of normal cell turnover (apoptosis), or a combination of the two.[34,35,36] This process is controlled by the principal prostatic androgen, DHT, which is produced when the principal circulating androgen, testosterone, is reduced within the stromal or endothelial tissues of the prostate by the enzyme 5α-reductase (See Figure 1).[37] In the prostate, DHT is about twice as potent as testosterone and has five times slower dissociation from the androgen receptor than testosterone.[38,39] DHT in the serum, which is derived from testosterone through conversion by both type 1 and type 2 5α-reductase, may play a role in maintaining prostatic enlargement.[40]

Figure 1. Diagram of Homeostasis between Cellular Proliferation and Cellular Death in the Prostate Leading to the Imbalance Hypothesized to Underlie BPH [37]



Isoenzymes of 5 alpha-reductase

Three forms, or isoenzymes of 5α-reductase are known to exist. Isoenzymes are proteins that have similar, but not identical, amino acid sequences.[41] Type 1 5α-reductase is expressed primarily in the skin and liver, but is also present in the prostate. Type 2 5α-reductase is the dominant isoenzyme in genital tissues including the prostate, but is also present in the skin and liver. Although early studies did not observe the presence of type 1 isoenzyme in the prostate, more recent studies using more sensitive assays indicate that both type 1 and type 2 mRNA protein and enzymatic activity are present in prostate tissues.[42,43,44,45] In one study, mRNA expression for both types 1 and 2 was slightly, but significantly increased in BPH tissue, when compared to the levels observed in normal prostate tissue. The same study showed that in the liver, type 2 mRNA was expressed at levels similar to those measured in BPH tissue. while type 1 mRNA expression was ten times higher.[45] Recently, a type 3 5α-reductase isoenzyme was discovered.[46] Preliminary data suggests that this isoenzyme is overexpressed in hormone-refractory prostate cancer, but has little or no expression in normal adult organs.

3.3 Risk Assessment for Benign Prostatic Hyperplasia

Risk factors for the progression of BPH include advancing age, the presence of androgens, increased prostate volume (PV), and serum PSA values.[47,48] Obtaining a medical history from men with urinary symptoms is an important step in assessing whether symptoms are due to BPH or to some other process.

The three overlapping clinical features of BPH are benign prostatic enlargement (BPE), bladder outlet obstruction (BOO), and lower urinary tract symptoms (LUTS). A detailed medical examination should focus on the urinary tract, previous surgical procedures, as well as health and fitness issues. A complete physical exam, including a digital rectal examination (DRE) should also be performed. Included in the assessment should be 1) urinalysis to rule out urinary tract infections (UTI) and hematuria, 2) serum creatinine measurement to assess renal function, and 3) serum PSA value to rule out prostate cancer.[48]

Symptoms from BPH can significantly impact quality of life and functional health status since symptom severity is generally what brings the patient to see the doctor.[18] Rating a patient's symptoms is very subjective; therefore, a questionnaire is often used to help standardize the assessment. One common questionnaire, developed by the American Urologists Association (AUA), is a symptom index (AUA-SI) that is completed by the patient. A series of seven questions are answered concerning the severity of symptoms that the patient is experiencing, such as incomplete emptying, frequency, intermittency, urgency, weak stream, straining, and nocturia. This questionnaire allows patients to rate symptoms on a scale of 0 to 5. The total point score is then matched to a point range to determine whether the patient's symptoms are mild (0 - 7 points), moderate (8 -19 points), or severe (20 - 35 points). These scores are useful in determining treatment planning and follow-up evaluations.[48]

A similar symptom index, developed by the World Health Organization, is known as the International Prostate Symptom Score (IPSS). The IPSS was adapted from the AUA-SI for use internationally. Patients answer a series of seven questions rating symptoms on a scale of 0 to 5. This questionnaire also includes an overall quality of life question. The IPSS generates a score, similar to AUA-SI, to determine a patient's symptom severity: mild (0 – 7 points), moderate (8 – 19 points), or severe (20 – 35 points).

Another assessment tool used is the BPH Impact Index (BII), which is used to assess the degree to which the symptoms affect the patient's daily activity and quality of life. The BII consists of four questions that evaluate how the patient's BPH symptoms affect physical discomfort, worry, bothersomeness, and limitations in activities of daily living. The total BII score is the sum of the four questions and ranges from 0 to 13.[18] A change in BII score of >0.5 is required to indicate that the therapy the patient is receiving is, in fact, reducing the negative impact of BPH (Minimum Perceptible Difference, MPD).[49]

The clinical manifestation of BPH includes prostate enlargement and signs of prostatic obstruction; however, there is no direct correlation between prostate size and symptoms of disease. For example, men with small prostates may experience severe obstruction and men with very large prostates may not exhibit signs of obstruction.[50]

Clinical Study

In a population-based, random survey of 1,709 men aged 40-70 years, data were analyzed to determine risk factors for a clinical diagnosis of BPH.[51] At baseline, men who reported having BPH were older, physically inactive, took antihypertensives/heart disease medications (especially beta-blockers), and had elevated total and free PSA levels. The odds of developing clinical BPH were doubled in the presence of heart disease, while the age-adjusted odds increased to 80% in men treated with beta-blocker medications. Furthermore, men with the highest free PSA levels had a 5 times greater risk of developing BPH than those in the lower quartiles.

CLINICAL PRESENTATION

Symptoms of BPH

Symptoms of BPH appear to be caused by either obstruction or spasmodic contractions of smooth muscle.[20] Development of BPH consists of two components: static and dynamic. The static, or mechanical, component is represented by hyperplasia of prostatic tissue. The tissue growth can lead to an increase in prostate size and subsequent urethral obstruction. The dynamic component is represented by the tone, or degree of constriction, of prostatic smooth muscle cells in BPH tissue.[18]

Lower Urinary Tract Symptoms (LUTS)

Many symptoms of BPH develop from obstruction of the urethra and gradual loss of bladder function, which results in incomplete emptying of the bladder. LUTS associated with BPH are typically divided into those associated with obstruction (voiding symptoms) and those associated with bladder irritation

(storage symptoms). It is possible for individual symptoms to be caused by both obstruction and irritation. Obstructive (voiding) symptoms include a weak urinary stream, prolonged voiding, abdominal straining, hesitancy, intermittency, incomplete bladder emptying, and terminal/postvoid dribbling. Irritative (storage) symptoms include frequency, nocturia, urgency, and urge incontinence.[52]

Benign Prostatic Enlargement (BPE)

Prostate size helps in assessing risks of such long-term complications, such as AUR and the need for BPH-related surgery.[53,54] The Olmsted County, Minnesota study of BPH concluded that the prostate grows by approximately 2% per year (on average), or about 20% per decade. However, a higher baseline prostate volume was associated with higher rates of prostate growth.[55]

Bladder Outlet Obstruction (BOO)

The obstruction in urine flow that often occurs with BPH is directly related to the anatomic location of the prostate gland. The enlarged prostate tissue presses inwardly, causing a partial obstruction of the urethra, thereby inhibiting urine flow. The size of the interior channel through the prostate, rather than the overall size of the prostate gland, better determines the mechanical obstruction to urine flow.[53,56]

In the early stages of BOO, the bladder wall compensates by thickening (adaptive hypertrophy). As this continues, the bladder will not be able to completely empty because of weakened detrusor muscles. Further complications include difficulty starting urination, a weak stream, and the complete inability to urinate (acute urinary retention).[57]

3.4 Diagnosis of Benign Prostatic Hyperplasia

DIAGNOSTIC ASSESSMENTS

Usually performed by a primary care physician or urologist, the initial evaluation of men with LUTS includes a detailed medical history, physical examination, symptom assessment, urinalysis, and the measurement of PSA.[16] An appropriate treatment plan may be developed if a diagnosis of BPH is suggested based on the initial evaluation. If abnormal findings are revealed in the initial evaluation, the patient may be referred to a urologist for further tests.

Medical History

A detailed medical history for men with BPH symptoms should focus on past medical history assessment of the urinary tract, previous surgeries, and general health issues. Physicians may evaluate whether the patient has a history of hematuria, urinary tract infections, diabetes, urethral strictures, or diseases of the nervous system. Furthermore, a thorough medical history should be evaluated to determine if the patient is taking any medications that may impair bladder contractility (such as anticholinergics) or increase the resistance to urinary outflow (i.e., sympathomimetics).[16]

Physical Examination

A complete physical examination should evaluate the presence or absence of a distended bladder, urethral discharge, genital abnormalities, and any neurological dysfunction that could affect voiding. An important portion of the physical exam is the digital rectal examination (DRE), where the prostate gland and surrounding tissues are palpated through the rectal wall to determine the size, consistency, shape, and symmetry of the gland. Due to the prevalence of prostatic disease in older men, many physicians routinely conduct a DRE during annual physical examinations of their male patients 50 years of age and older.[16,26,56]

PSA Test

A PSA test is also an important part of the initial evaluation. PSA is a glycoprotein produced by epithelial cells lining the glands and ducts of the prostate gland. PSA is mainly concentrated in prostatic tissue and in small amounts in the bloodstream. Serum PSA levels are normally very low; however, PSA spills into the bloodstream and serum levels rise when diseases such as BPH, prostatitis, or prostate cancer are present.[26] Measurement of the serum PSA concentration is the most accurate method for the detection of prostate cancer, and should be performed on an annual basis for all men beginning at 50 years of age and older or 45 years of age and older for men at high risk, such as those with a first-degree relative having prostate cancer or African American men.[26,53,58,59] Normal PSA values range from 0 to 4 ng/mL.

The total PSA concentration is composed of the free and bound PSA. Evaluation of the free and total concentrations is helpful, since benign prostate tissue produces a higher percentage of free PSA than does cancerous tissue. Thus, in patients with prostate cancer, the free to total ratio of PSA is lower whereas this ratio is higher in patients with BPH.[60]

Other Diagnostic Tests

Further diagnostic tests by a urologist may be warranted if the diagnosis remains unclear after the aforementioned tests. Some of these tests may include uroflowmetry, which measures maximum flow rate (Q_{max}) and total flow time. Men with BPH have reduced Q_{max} and prolonged flow time.[16,26,53,61] Postvoid residual urine volume (PVR) remaining in the bladder, measured by catheterization or ultrasound, may be increased in men with BPH.[53,61] The urethra and bladder can be viewed by cytoscopy, where a cytoscope is inserted directly into the urethra. Finally, transrectal ultrasonography (TRUS) uses an ultrasound probe inserted into the rectum to help assess the size, texture, and density of the prostate.[53]

3.5 Approaches to Benign Prostatic Hyperplasia Treatment

Approaches to Treatment

Practice guidelines have been developed to help practitioners with the daily clinical management of BPH. U.S. guidelines on BPH were developed by the Agency for Healthcare Policy and Research (AHCPR) and published in 1994.[48] The development process involved a detailed review of published literature on BPH diagnosis and treatment. Before publication, experts and practitioners in the fields of urology, internal medicine, and family practice extensively reviewed the draft guidelines.

The International Consultation (IC), supported by the World Health Organization (WHO), is an international group of experts in prostatic diseases who develop recommendations for the diagnosis and treatment of BPH. Using a "consensus approach", they also base their recommendations on a detailed review of published literature.[5]

Current goals of BPH therapy include identifying patients at risk through appropriate diagnosis, improving American Urological Association Symptom Index (AUA – SI) scores, improving patient health status, decreasing the risk of AUR and BPH-related surgeries, and slowing progression of disease. This leads to reduced symptoms and improved quality of life.[5]

Several treatment options are available to treat BPH. The most common treatment strategies include watchful waiting, pharmacological management, and surgery. Other therapies include balloon dilation of the prostate, electrical vaporization, transurethral microwave thermotherapy (TUMT), transurethral needle ablation of the prostate (TUNA), and herbal supplements. The specific treatment choice is dependent upon symptom severity, the patient's perception of the significance of the symptoms, and the benefits and risks of each treatment.[5,48]

Once a patient is diagnosed and categorized according to symptom severity (AUA-SI), the guidelines suggest that patients with severe symptoms (AUA-SI score > 20) be treated with surgery. Patients with moderate symptoms (AUA-SI score 8 – 19) are candidates for pharmacological treatment, and those with mild symptoms (AUA-SI score 0 – 7) may be managed with watchful waiting.[5]

Treatment modalities may eventually fail to alleviate symptoms. Estimates of the five-year treatment failure rates vary based on the initial intervention (see Table 1). Open prostatectomy exhibits the lowest failure rate, whereas other treatments have a failure rate of about 10%. Confidence intervals are wide due to limited follow-up data, making differences difficult to assess. More recent studies have found lower failure rates for prostatectomy, transurethral resection of the prostate (TURP), and finasteride than reported using the Agency for Health Care Policy and Research (AHCPR) data. In addition, some smaller studies found a higher rate of transurethral incision of the prostate (TUIP) failure; however, larger studies need to confirm these results.[50]

Newer minimally invasive devices do not seem to be as durable as traditional surgery and medication. Retreatment rates for TUMT varied from 14.3% to 26.2% in studies with three to four years of follow-up, and about one-third of patients required retreatment in the 5-year follow-up.[50] Long-term results on laser treatment are mixed. While a laser coagulation study found 2.0% and 5.3% retreatment rates based on two to three year follow-up, a higher rate (18.1%) was reported in a 3-year laser vaporization study.[50]

However, the retreatment rate for the TURP comparator arm was 9.2%, which is higher than reported in other studies. Another study comparing transurethral vaporization of the prostate (TUVP) and TURP over a 2-year follow-up period found a retreatment rate of 7.7% for both groups.[50] Similarly, the 2-year follow-up information available for TUNA was 12.8%. Overall, recent studies suggest lower retreatment rates for conventional surgery (TURP, open prostatectomy) and medication than estimated by AHCPR, whereas relatively high retreatment rates were found for TUIP and the newer minimally invasive modalities.

Table 1. Five-Year Failure Rates for BPH Treatment Modalities[48]

Treatment	Failure Rate % (90%CI)
Surgery	
Open prostatectomy	2% (1-4)*
TURP	1% (9-11)†
TUIP	9% (1-28)‡
Device	
TUMT	14.3 - 26% in 3-4 year FU, 33% in 5 yr FU
Laser	2 - 18% in 2-3 year FU
Non-surgical options	
Alpha blockers§	13% (4-31)
Finasteride	10% (9-12)‖
Watchful waiting	38% (15-65)

* More recent studies showed lower risks, 5-year risk of 2.3% and 8-year risk of 3.3%; † Five-year failure rates were lower (3.9-4.8%) in more recent database studies with the 8 - >10 year follow-up failure rates were 6.6-7.9%; ‡ More recent small studies found higher failure rates than 9%;§ Low estimate, assuming the risk to level off after the first year; ‖ More recent data shows lower rates, 2-year failure of 4.2% and 4-year failure of 4.6%;

CI = confidence interval; FU = follow-up; TUIP = transurethral incision of the prostate; TUMT = transurethral microwave thermotherapy; TURP = transurethral radical prostatectomy.

Table 2. Non-Surgical Treatment Options[5,48,52]

Treatment Option	Description	Effect	Criteria for Use/ Patient Factors	Advantages	Limitations
Watchful Waiting	Strategy of monitoring for symptom progression and BPH complications on a periodic basis without active intervention.	The probability of disease progression is uncertain. Some patients experience reductions in symptom severity, while others experience worsening of symptoms.	Mild symptoms AUA-SI/IPSS Score 0 - 7	· Studies show that pharmacological interventions are not significantly more effective than placebo in these patients	· Spontaneous exacerbations and remissions of BPH (even without treatment) can occur in this population

Treatment Option	Description	Effect	Criteria for Use/ Patient Factors	Advantages	Limitations
Nonselective Alpha Blockers Doxazosin Prazosin Terazosin	Competitive antagonist of postsynaptic alpha-adrenergic receptors	Prevents the contraction of smooth muscle in the prostate, which contributes to bladder outflow obstruction. This results in relaxation of prostatic smooth muscle and improvement in both BPH symptoms and urinary flow rate.	Moderate symptoms AUA-SI/IPSS score 8 - 19	· Immediate improvement in BPH symptoms · Can be used in combination with other therapies as needed · Side effects can be minimized with bedtime dosing and slow titration	· Not selective for receptors in prostate · Considered less effective than surgery in improvement of AUA-SI scores · Significant side effect profile
Selective Alpha Blockers Tamsulosin Alfuzosin Silodosin	Selective antagonist of $alpha_{1a}$ adrenergic receptors in prostate	Prevents the contraction of smooth muscle in the prostate, which contributes to bladder outflow obstruction. This results in relaxation of prostatic smooth muscle and improvement in both BPH symptoms and urinary flow rate.	Moderate symptoms AUA-SI/IPSS score 8 – 19	· Immediate improvement in BPH symptoms · Can be used in combination with other therapies as needed · Potentially elective for prostate smooth muscle · Potentially, less hypotensive effects	· Less effective than surgery in improvement of AUA-SI scores · More expensive than nonselective alpha blockers

Treatment Option	Description	Effect	Criteria for Use/ Patient Factors	Advantages	Limitations
5 Alpha-Reductase Inhibitor Finasteride	Competitive inhibitor of 5 alpha- reductase isoenzyme type 2	Inhibits the conversion of testosterone to DHT. This results in a reduction in serum DHT, thereby decreasing prostate volume, improving urinary flow and BPH symptoms, and reducing risk for AUR and need for BPH-related surgery.	Moderate symptoms AUA-SI/IPSS score 8 – 19 Men with enlarged prostates	· Relieves symptomatic BPH · Risk reduction of AUR and need for BPH- related surgery · Slows disease progression · Can be used in combination with the alpha-blocker, doxazosin, to reduce the risk of symptomatic progression	· May take 3 – 6 months to see clinical effect
5 Alpha-Reductase Inhibitor *Avodart* (dutasteride)	Competitive inhibitor of 5 alpha-reductase isoenzyme types 1 and 2	Inhibits the conversion of testosterone to DHT. This results in a reduction in serum DHT, thereby decreasing prostate volume, improving urinary flow and BPH symptoms, and reducing risk for AUR and need for BPH-related surgery.	Moderate symptoms AUA-SI/IPSS score 8 - 19 Men with enlarged prostates	· Relieves symptomatic BPH · Risk reduction of AUR and need for BPH-related surgery · Slows disease progression · Can be used in combination with the alpha-blocker, tamsulosin, to reduce the risk of symptomatic progression	· May take 3 – 6 months to see clinical effect

Table 3. Surgical Treatment Options[5,48,52]

Surgical Treatments	Description	Criteria for Use/ Patient Factors	Advantages	Limitations
Open Prostatectomy	Surgical removal of the inner portion of the prostate	Reserved for patients with: · Very large prostate gland · Structural problems · Bladder calculus · Urethral diverticulum	· Most effective treatment for relieving symptoms · Tissue sample obtained to assess for malignancy	· Most invasive treatment · Associated with most morbidity · Complications such as blood transfusions, bladder neck contracture, urethral stricture, and sexual dysfunction

TURP Transurethral resection of the prostate	Removal of prostatic tissue using a device inserted through the urethra	· Severe symptoms · Failed medical or device treatment	· Reported to reduce symptoms in 88% of patients · Tissue sample obtained to assess for malignancy	· Long-term complications such as retrograde ejaculation, impotence, partial or total incontinence · Approximately 10% of patients require retreatment within five years · Costly procedure
TUIP Transurethral incision of the prostate	Endoscopic procedure using only one or two incisions to reduce constriction of the urethra without removing any of the prostate gland	· Poor surgical candidates · Severe symptoms · Prostate glands < 50 or 60g in total weight · May be preferred when fertility and ejaculation are important	· Can be performed as outpatient procedure · Minimally invasive · Lower cost and less morbidity than TURP	· Long-term satisfaction and retreatment rates have not been adequately studied
TUMT Transurethral microwave thermotherapy	Microwave antenna is placed in a urethral catheter. Microwave causes deep, rapid tissue heating	· Poor surgical candidates · Severe symptoms · Patients who find the risk of sexual dysfunction associated with TURP to be unacceptable	· Short outpatient procedure · No major complications · Limited studies show 65% decrease in symptoms and 45% improvement in urinary flow rates	· 7.3% of patients at 2 years post treatment (14.3-26% in 3-4 year FU, 33% in 5yr FU) require retreatment · No tissue is obtained, therefore it is not possible to assess for malignancy
TUVP Transurethral vaporization of the prostate	Endoscopic electrosurgical procedure with ablation of the prostate by electrode or laser	· Poor surgical candidates · Severe symptoms · Patients who find the risk of sexual dysfunction associated with TURP to be unacceptable	· Provides symptom reduction similar to TURP	· 2-18% failure in 2-3 year FU · No tissue obtained, therefore not possible to assess patients for concurrent prostatic malignancy

TUNA Transurethral needle ablation of the prostate	Placement of radiofrequency needles in prostate	· Poor surgical candidates · Severe symptoms · Patients who find the risk of sexual dysfunction associated with TURP to be unacceptable	· Relatively safe procedure · Performed without using local anesthesia	· Results may be limited, because the bladder neck and median prostate lobe can not be treated
Transurethral balloon dilation w/ stents	Balloon dilation of the prostate. Urethral stents can be placed to maximize success of the dilation.	· High risk surgical candidates with short life expectancy	· Minimally invasive · Relatively safe procedure	· High retreatment rate · Stents susceptible to infection

4. PRODUCT DESCRIPTION

4.1 Generic Name, Brand Name and Therapeutic Class

Generic Name: dutasteride

Brand Name: Avodart®

Therapeutic Class: 5 Alpha-Reductase Inhibitor

4.2 Dosage Forms, Package Sizes, and NDC

Avodart Soft Gelatin Capsules 0.5 mg are oblong, opaque, dull yellow, gelatin capsules imprinted with "GX CE2" in red ink on one side packaged in:[6]

- Bottles of 90 with child-resistant closures (NDC 0173-0712-04)
- Bottles of 30 with child-resistant closures (NDC 0173-0712-15)

4.3 AHFS or Other Drug Classification

DPS/AHFS Classification: 92:00 Unclassified Therapeutic Agents

4.4 FDA Approved Indications

Avodart is indicated for the treatment of symptomatic benign prostatic hyperplasia (BPH) in men with an enlarged prostate to:[6]

- Improve symptoms
- Reduce the risk of acute urinary retention
- Reduce the risk of the need for BPH-related surgery

Avodart in combination with the alpha-blocker tamsulosin is indicated for the treatment of symptomatic BPH in men with an enlarged prostate.

4.5 Use in Special Populations

Refer to Enclosed Prescribing Information.

4.6 Pharmacology

Refer to Enclosed Prescribing Information.

4.7 Pharmacokinetics/Pharmacodynamics

PHARMACOKINETICS

Absorption

Peak serum concentrations of *Avodart* occur within 1 to 3 hours following administration of a single dose of *Avodart* 0.5 mg.(62) Absolute bioavailability of *Avodart* in healthy subjects is approximately 60% and is not affected by food.

Distribution

Pharmacokinetic data following single and repeat oral doses show that *Avodart* has a large volume of distribution (300 to 500 L). (62) *Avodart* is highly bound to plasma proteins (>99.5%).

Following daily dosing, *Avodart* serum concentrations achieve 65% of steady-state concentration after one month and approximately 90% after three months.(62) The average steady-state serum *Avodart* concentration was 40 ng/mL following 0.5 mg daily for 6 months. Similar to serum, concentrations in semen achieved steady state at 6 months. After 12 months of therapy, semen *Avodart* concentrations averaged 3.4 ng/mL (range 0.4 to 14 ng/mL). On average, 11.5% of serum *Avodart* concentrations partitioned into semen.

Metabolism and Elimination

Avodart is extensively metabolized in humans.(62) In vitro, *Avodart* is metabolized by the cytochrome P450 CYP3A4 isoenzyme. *Avodart* is not metabolized by cytochrome P450 isoenzymes CYP1A2, CYP2C9, CYP2C19, or CYP2D6. In human serum, following dosing to steady state, unchanged dutasteride, three major metabolites (4′-hydroxydutasteride, 1,2-dihydrodutasteride, and 6-hydroxydutasteride), and two minor metabolites (6,4′-dihydroxydutasteride and 15-hydroxydutasteride), have been detected as assessed by mass spectrometric response. The absolute stereochemistry of the hydroxyl additions in the 6 and 15 positions is unknown.

Avodart is extensively metabolized in humans.(62) Dutasteride and its metabolites are excreted mainly in feces. As a percent of dose, there was approximately 5% unchanged dutasteride (~1% to 15%) excreted. The remainder is excreted as dutasteride-related metabolites. Only trace amounts of unchanged dutasteride were found in urine (< 1%).

Dutasteride at concentrations >3 ng/mL is cleared slowly primarily by linear, non-saturable elimination.(62) The terminal elimination half-life is approximately five weeks at steady-state. Due to the long half-life of *Avodart*, serum concentrations remain detectable (greater than 0.1 ng/mL) for up to four to six months after discontinuation of treatment.

Effect on Serum Dihydrotestosterone (DHT) Concentrations

In patients with BPH treated with *Avodart* 0.5 mg daily for two years, the median decrease in serum DHT was 94% at one year and 93% at two years.(62) During the 2-year open-label extension studies, the median decrease in serum DHT was 95% at both 3 and 4 years.(63,64,65)

Significant adjusted mean decreases of ≥90% ($P < 0.001$) in serum DHT were noted in a subgroup of patients from each study (n = 65 per treatment group in each study, total N = 195 for the three studies combined) as early as one month and continued through the 24 months of therapy (see Table 4).(13,14,15)

Table 4. Median % (±SD) Change from Baseline in Serum DHT Concentrations with *Avodart* 0.5 mg Daily (LOCF)[13,14,15]

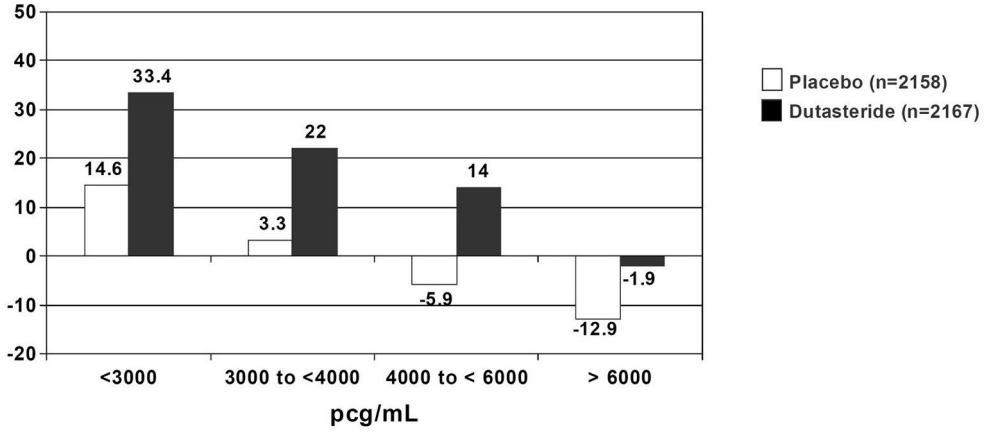
Time point	*Avodart* n = 195	Placebo n = 195
1 month	-91.0 (± 15)	9.2 (± 51)
3 months	-92.7 (± 15)	11.2 (± 52)
6 months	-93.5 (± 16)	13.0 (± 47)
12 months	-94.3 (± 19)	4.3 (± 39)
18 months	-94.2 (± 22)	5.0 (± 42)
24 months	-93.7 (± 21)	6.1 (± 54)
DHT=dihydrotestosterone; LOCF = last observation carried forward; SD = standard deviation		

Effect on Serum Testosterone Concentrations

The median increase in serum testosterone concentrations was 19% for men who received *Avodart* at both one and two years during the three pooled pivotal studies.[62] For men who received placebo, the median increase in serum testosterone and 1.4%.[13,14,15] Despite higher mean serum testosterone concentrations in patients receiving *Avodart*, these values remained within the limits of the normal limits (< 10,000 pcg/mL) for more than 99% of men at the end of 2 years of treatment. [66]

A post-hoc analysis of the data by baseline serum testosterone values revealed that patients with the lowest baseline concentrations experienced the largest increases in serum testosterone, while those with normal-to-high baseline values had more modest increases in testosterone (see Figure 2).[13,14,15] However, this information should be interpreted cautiously, since the time of day of sample collection was not standardized throughout the studies. The median increase in serum testosterone was 26% at 3 years and 22% at 4 years from the open-label extension studies.[63,64,65] These serum levels of testosterone also remained within the normal physiologic range.

Figure 2. Median Percent Change in Baseline Serum Testosterone after *Avodart* 0.5 mg Daily or placebo for 24 months[13,14,15]



4.8 Contraindications

Refer to Enclosed Prescribing Information.

4.9 Warnings/Precautions

Refer to Enclosed Prescribing Information.

4.10 Adverse Events

Refer to Enclosed Prescribing Information.

4.11 Other Clinical Considerations

Refer to Enclosed Prescribing Information.

4.12 Drug/Food/Disease Interactions

Refer to Enclosed Prescribing Information.

4.13 Dosing and Administration

Refer to Enclosed Prescribing Information.

5. EFFICACY AND SAFETY TRIALS

5.1 Double-Blind Phase of Pivotal Trials

Monotherapy Clinical Trials

Three randomized, double-blind, placebo-controlled, parallel clinical trials evaluated the safety and efficacy of *Avodart* 0.5 mg daily for 2 years in the treatment of 4,325 men (mean age, 66 years) with benign prostatic hyperplasia (BPH) and disease management followed by corresponding 2-year open-label study extensions.[7,13,14,15] Patients enrolled in these trials were males ≥50 years of age with a diagnosis of BPH according to medical history and physical exam, including: digital rectal exam (DRE), American Urological Association Symptom Index (AUA-SI) score ≥12 (out of a total possible score of 35), maximum urinary flow rate (Q_{max}) of ≤15 mL/s (milliliter per second) with a minimum voided volume of ≥125 mL, and a total prostate volume (PV) of ≥30 cc as determined by transrectal ultrasound (TRUS). Patients were excluded if their post-void residual volume was >250 mL or if their serum prostate specific antigen (PSA) was <1.5 or >10.0 ng/mL. Patients using any form of phytotherapy (including saw palmetto) within 8 weeks or those with a historical use of finasteride were excluded from participating in the trials. Patients initially completed a single-blind 4-week placebo run-in period prior to randomization to evaluate initial improvements in lower urinary tract symptoms (LUTS) and urinary flow rates after treatment with placebo, as has been previously reported with other studies evaluating BPH therapy.[67]

The primary efficacy parameter at 2 years was the incidence of acute urinary retention (AUR).[7] Secondary endpoints included the incidence of BPH-related surgical intervention, and changes from baseline in: AUA-SI score, PV, and Qmax. Serum dihydrotestosterone (DHT), testosterone, and luteinizing hormone (LH) concentrations and a selected health status measure (BPH Impact Index or BII) were also evaluated at various time points.[13,14,15] The BII ranges from 0 to 13, with higher values indicating poorer quality of life.[12]

The results described for the 2-year double-blind phase are based upon last observation carried forward (LOCF) analyses and represent pooled data across the 3 trials for the intent-to-treat patient population, unless otherwise stated.[13,14,15] Separate analyses using “at last visit” values yielded consistent results, which have been published.[7]

Demographic and Baseline Characteristics

All 4,325 randomized subjects were male and were primarily Caucasian. [7,13,14,15] The mean age of the study population was 66 years, the mean duration of BPH symptoms was approximately 5 years (median: 4 years), and the mean time since BPH diagnosis was 3 to 4 years (median: 2 years). Baseline characteristics were comparable across treatment groups for all three studies.

The mean and median prostate volumes at baseline were 54.0 cc (mL) and 48.3 cc, respectively, in the placebo group and 54.9 cc and 48.7 cc, respectively, in patients treated with *Avodart*. The largest prostate volume enrolled in the trial was 259.1 cc. After the 4-week placebo run-in, the mean baseline AUA-SI score was approximately 17 units across the 3 studies. The mean Q_{max} at baseline across the three studies was approximately 10 mL/s.

Completion and Withdrawal Rates in the 2 year Monotherapy Clinical Studies

Patients were initially randomized to receive either *Avodart* 0.5 mg daily (n = 2167) or placebo (n = 2158).[7] Most of the 4,325 subjects randomized completed the 24 months of treatment (67% of those receiving *Avodart* and 70% of placebo patients, respectively).

The primary reasons for discontinuation from the first 2 years of the study included lack of efficacy, adverse events, and withdrawn consent.[7] Similar proportions of patients receiving placebo and *Avodart* were withdrawn from the studies due to adverse events (9% in each treatment group).[13,14,15] However, a higher proportion of patients receiving placebo were withdrawn due to lack of efficacy compared with the patients who received *Avodart* (10% and 6%, respectively).

BPH-Related Surgical Intervention

Compared with placebo, treatment with *Avodart* was associated with a significant 48% reduction in the risk of BPH-related surgical intervention (incidence: 4.1% for placebo vs. 2.2% for *Avodart*) over the 24-month study ($P < 0.001$, 95% CI; 0.26, 0.63), which corresponded to a relative risk of BPH-related surgery of 52%.[13,14,15]

Incidence of AUR

A patient was considered to have AUR if he was unable to urinate and required bladder catheterization. During the first 2 years, 90 patients (4.2%) experienced AUR in the placebo treatment group compared with 39 patients (1.8%) who received *Avodart* ($P < 0.001$). The risk of AUR in patients treated with *Avodart* was 43% ($P < 0.001$, 95% CI; 0.29, 0.62), corresponding to a risk reduction of 57% relative to the placebo group.[7,13,14,15]

Combined Endpoint of AUR Incidence or BPH-Related Surgical Intervention

Avodart significantly lowered the risk for the combined endpoint of AUR or the need for BPH-related surgical intervention by 49% (incidence: 6.8% for placebo vs. 3.5% for *Avodart*; $P < 0.001$, 95% CI; 0.38, 0.67) (Table 5). The differences between treatment groups increased over time.[13,14,15]

Table 5. Cumulative Number of Patients and Time to First Occurrences of Experiencing AUR or BPH-related Surgical Intervention by Treatment[13,14,15]

	0-6 Months	6-12 Months	12-18 Months	18-24 Months
Avodart (n = 2167)				
# of Events	25	44	61	75 (3.5%)*
# Patients at risk	2167	2052	1928	1827
Placebo (n = 2158)				
# of Events	34	73	104	146 (6.8%)*
# Patients at risk	2158	2039	1919	1793

AUR = acute urinary retention; BPH = benign prostatic hyperplasia; * $P < 0.001$ for *Avodart* relative to placebo.

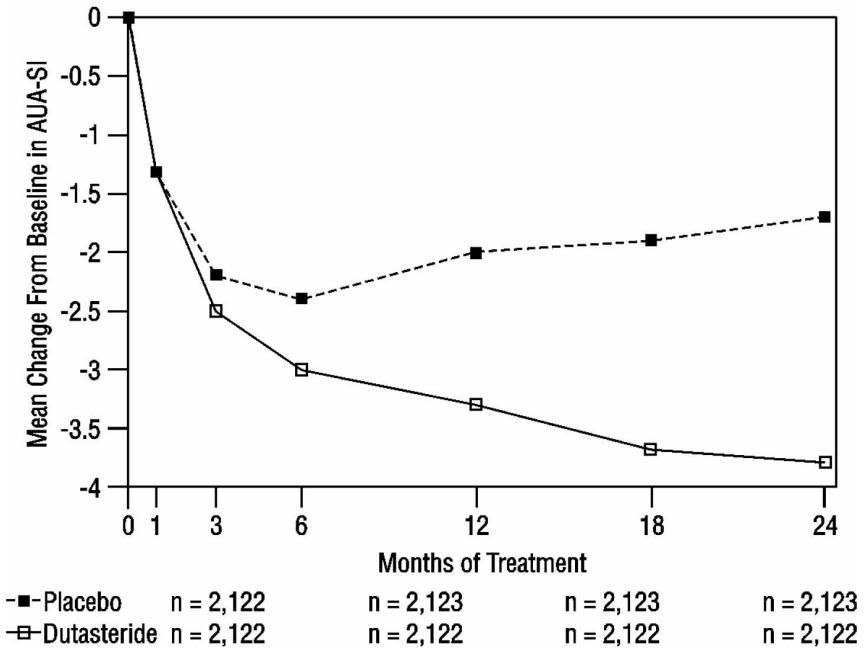
AUA-SI Scores

Symptoms were evaluated using the AUA-SI score, a questionnaire that evaluates urinary symptoms (incomplete emptying, frequency, intermittency, urgency, weak stream, straining, and nocturia) by rating each symptom on a 0 to 5 point scale, for a total possible score of 35.[68] After the 4-week placebo run-in phase, the mean baseline AUA-SI score was approximately 17 units across the 3 studies.[7,13,14,15]

Patients treated with *Avodart* showed significant improvement in symptoms beginning by month 3 in one study and by 12 months in the other two studies. At month 12, the pooled mean decrease from baseline in AUA-SI score was –3.8 units for *Avodart* and –2.0 units for placebo with a mean difference between treatment groups of –1.3 (range: –1.1 to –1.5 units in each of the 3 studies, $P < 0.001$), a value that was consistent across the studies.

At month 24, the mean decrease from baseline in AUA-SI score was –3.8 units for *Avodart* and –1.7 units for placebo, with a mean difference between treatment groups of –2.1 ($P < 0.001$) (Figure 3).

Figure 3. AUA-SI Score Change from Baseline (Monotherapy Studies Pooled, LOCF) (13,14,15)



Total Prostate Volume (TPV)

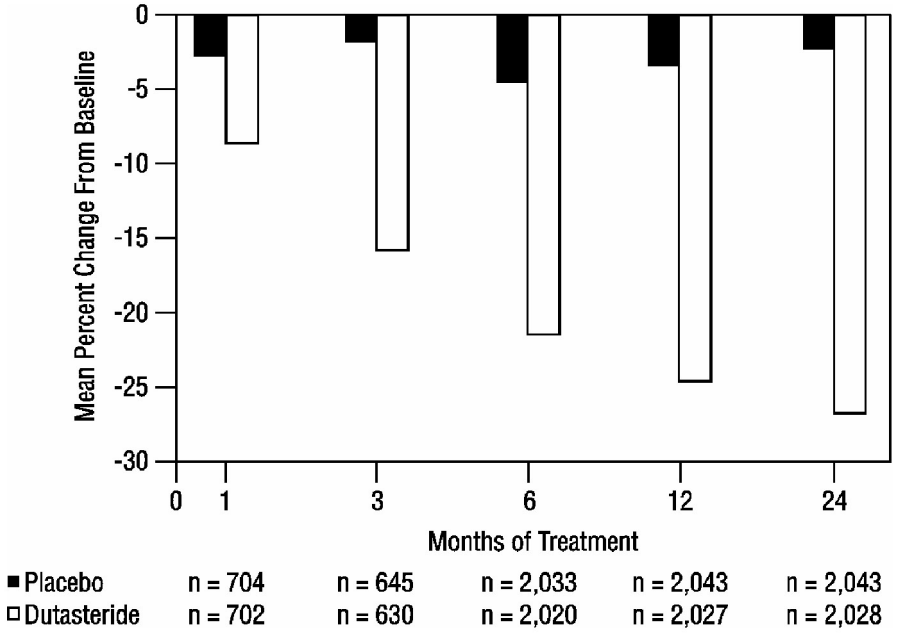
In patients receiving *Avodart*, a significant reduction in TPV ($P < 0.001$) was achieved by the earliest post-treatment measurement in each study (month 1 in study 1, month 3 in study 2, and month 6 in the third study), and continued through 24 months in all 3 studies (Table 6).(13,14,15)

Table 6. Adjusted Mean Percent Change From Baseline in Total Prostate Volume at Various Time Points after Therapy with *Avodart* 0.5 mg Daily or Placebo for 24 months (LOCF) (13,14,15)

Time Point	*Avodart* (N = 2167)	Placebo (N = 2158)	*P* value* (95% CI)
1 month	–8.6	–2.9	< 0.001 (–7.6, –3.7)
3 months	–15.9	–1.9	< 0.001 (–15.9, –12.2)
12 months	–24.7	–3.4	< 0.001 (–22.6, –20.0)
24 months	–26.7	–2.2	< 0.001 (–25.9, –23.1)
**Avodart* versus placebo, adjusted for baseline; CI = confidence interval			

The adjusted mean difference between treatments was –24.5% (range: –24.0% to –25.1% in each of the three studies; $P < 0.001$).(13,14,15) At month 24, the pooled adjusted mean percent decrease in prostate volume across the three studies was –26.7% for patients receiving *Avodart*and –2.2% for those receiving placebo (see Figure 4).

Figure 4. Total Prostate Volume Percent Change from Baseline (Monotherapy Studies Pooled, LOCF) [13,14,15]



Prostate Transitional Zone Volume (TZV)

The pooled adjusted mean reduction from baseline TZV at 24 months was –24.3% in patients receiving *Avodart* compared with an increase of +10.4% in those receiving placebo ($P < 0.001$, 95% CI; –29.8, –24.3). [13,14,15] TZV was also reduced in patients receiving *Avodart* beginning at one month of therapy and continuing throughout the 24-month study.

Maximum Urinary Flow Rates (Qmax)

The mean baseline Q_{max} was approximately 10 mL/s across the three monotherapy studies.[7] Differences in Q_{max} between treatment groups were statistically significant from baseline at month 13 in all three studies and were maintained through month 24. At month 12, the mean increase in Q_{max} was 1.9 mL/s for *Avodart* and 0.6 mL/s for placebo, with a mean difference between treatments of 1.3 mL/s ($P < 0.001$). At month 24, the mean increase in Q_{max} was 2.2 mL/s for *Avodart* and 0.6 mL/s for placebo, with a mean difference of 1.6 mL/s ($P < 0.001$).

Serum Endocrine Parameters (Dihydrotestosterone [DHT], Testosterone, and Luteinizing Hormone [LH])

Baseline mean serum DHT concentrations ranged from 415 to 428 pg/mL.[7] At 24 months, the median percent reduction in DHT serum concentration was 93.7% for all patients receiving *Avodart*. Significant adjusted mean decreases of ≥90% ($P < 0.001$) in serum DHT were noted in a subgroup of patients from each study (n = 65 per treatment group in each study, total N = 195 for the three studies combined) as early as one month and continued through the 24 months of therapy.[69]

The median increase in serum testosterone concentration at 24 months was 19% for patients receiving *Avodart* and 1.4% for patients receiving placebo. [66] Despite higher serum testosterone concentrations in patients receiving *Avodart*, the mean and median values remained within limits of the normal range (<10,000 pcg/mL [pg/mL]) for both groups of patients.

LH concentrations were measured in one of the monotherapy trials.[14] At baseline, median LH measurements were 4.4 IU/L in both treatment groups. The median percent increase in LH concentration in patients receiving *Avodart* was 12% at 6 months and 19% at both 12 and 24 months. Median change from baseline at month 24 was 0.8 IU/L in patients receiving *Avodart* and 0.2 IU/L in patients receiving placebo.

Effect on BPH Impact Index (BII) in monotherapy trials

The BPH Impact Index (BII) is a quality of life tool that measures the effect that BPH has on physical discomfort, worry, level of bother and impact on normal activities on a scale of 0 to 4 for each question.[12] A change in BII score of ≥ 0.5 is considered necessary for a minimum perception by patients that the therapy they are receiving is indeed reducing the negative impact of BPH. The BII was assessed at baseline and at Months 1, 3, 6, 12, 18, and 24.[13,14,15] *Avodart* significantly improved the health status of patients treated with *Avodart* compared with placebo, as demonstrated by a mean difference in the BII score of –0.74 for patients receiving *Avodart* (range:–0.74 to –0.81) and +0.03 for those receiving placebo ($P < 0.001$).[13,14,15]

Voiding Efficiency

Patients treated with *Avodart* and placebo had similar mean voided efficiencies at baseline. Compared to placebo, voiding efficiencies were significantly greater with *Avodart* over the 2-year period. Patients treated with *Avodart* had an increase of 2.7% between baseline and endpoint versus a decrease of 0.8% observed with patients treated with placebo. Although there was an initial increase in efficiency, disease progression was observed over time in those patients treated with placebo (Table 7).[70]

Table 7. Adjusted Mean Voiding Efficiency (%)* (Intent-to-treat Population) [70]

Assessment	*Avodart*	Placebo	*P*- value
Baseline	78	78.2	0.69
Month 1	78.4	78.6	0.79
Month 6	79.7	78.5	0.02
Month 12	80.4	78.2	< 0.001
Month 24	80.7	77.4	< 0.001
*Voiding Efficiency calculated as: [volume voided at assessment timepoint/ volume voided at baseline + post-void residual volume] [(%)]			

Response to Treatment Based Upon Baseline Prostate Volume

Only patients with a baseline prostate volume ≥ 30 cc were enrolled in these clinical trials. Among these patients, results of the trials were analyzed according to smaller baseline prostate size (30 to 39 cc) and compared with those observed in patients with larger baseline prostate size (≥ 40 cc).[13,14,15]

Improvements in efficacy endpoints occurred in patients with both smaller and larger baseline prostate sizes (Table 8). *Avodart* reduced the risk of AUR and BPH-related surgical interventions in all patients, regardless of baseline prostate volume. Of note, the results indicated that patients with larger baseline PV (≥ 40 cc) were more likely to experience AUR or BPH-related surgical intervention than those with smaller baseline prostate volumes (Table 8).[13,14,15]

Table 8. Efficacy in Patients Receiving *Avodart* and Placebo at 24 Months Based on Baseline Total Prostate Volume[13,14,15]

Parameter	Prostate Volume 30 to 39 cc		Prostate Volume ≥ 40 cc	
	Placebo (n = 602)	*Avodart* (n = 621)	Placebo (n = 1546)	*Avodart* (n = 1538)
Number of patients experiencing AUR	13 (2.2%)	2 (<1%)	77 (5.0%)	35 (2.3%)
Number of patients requiring BPH-related surgery	18 (3.0%)	12 (1.9%)	70 (4.5%)	34 (2.2%)
Mean change from baseline* in prostate volume (%)	–2.5%	–26.1%	–2.2%	–26.9%
Mean change from baseline* in Qmax (mL/sec)	0.7	1.7	0.7	1.8
*adjusted mean (adjusted for baseline); AUR = acute urinary retention; BPH = benign prostatic hyperplasia; Qmax = maximum urinary flow rate				

Response to Treatment Based Upon Baseline PSA

When examining patients with baseline PSA concentrations < 3 ng/mL and ≥ 3 ng/mL, *Avodart* reduced the risk of AUR and BPH-related surgery in both groups. Consistent reductions in prostate volume and improvements in urinary flow were also noted regardless of baseline PSA concentration. Higher baseline PSA concentrations (≥ 3 ng/mL) predicted larger treatment differences in the subjective endpoints, like AUA-SI scores.[13,14,15]

Adverse Events

A total of 2167 patients were exposed to *Avodart* in the three clinical trials. [66] Most adverse events were mild or moderate and generally resolved while on treatment in both the *Avodart* and placebo groups.

Over the 2-year treatment period, 376 patients (9% in each treatment group) were withdrawn from the studies due to adverse experiences, most commonly associated with the reproductive system.[13,14,15] Withdrawals due to adverse events that were considered drug-related occurred in 4% of patients who received *Avodart* and 3% of placebo patients. A drug-related adverse event was an adverse event whose causality was recorded by the investigator as having a reasonable possibility that it might have been caused by the study drug. The exact mechanism for these events is unknown; but may be related to the androgenic effects of *Avodart*. Drug-related adverse events occurred in 19% of patients receiving *Avodart* compared with 14% of those receiving placebo, primarily due to a higher incidence of sexual adverse events or gynecomastia.[7] The overall incidence of drug-related sexual adverse events (impotence, decreased libido, ejaculation disorders, sexual function disorders) was 11% for patients receiving *Avodart* and 6% in placebo-treated patients.[13,14,15] Specifically, drug-related impotence was reported by 7.3% of patients receiving *Avodart* and 4.0% receiving placebo; decreased libido by 4.2% and 2.1%, respectively; and ejaculation disorder by 2.2% and 0.8%, respectively over the entire study.[7] Drug-related gynecomastia was reported in 2.3% of patients receiving *Avodart* and 0.7% of placebo-treated patients.

Table 9 summarizes the drug-related adverse events that occurred in at least 1% of patients receiving *Avodart* and at a higher incidence than those receiving placebo. [66] The incidence of new cases of drug-related sexual adverse events decreased over the study period, while the incidence of drug-related gynecomastia remained constant over the treatment period.

Table 9. Drug-related* Adverse Events Reported in ≥1% of Patients and More Frequently Among Patients Receiving *Avodart* vs. Placebo (Monotherapy Studies Pooled) (66)

Adverse Event Terms	Adverse Event Onset			
	Month 0-6	**Month 7-12**	**Month 13-18**	**Month 19-24**
Avodart	**(n = 2167)**	**(n = 1901)**	**(n = 1725)**	**(n = 1605)**
Placebo	**(n = 2158)**	**(n = 1922)**	**(n = 1714)**	**(n = 1555)**
Impotence				
Avodart	4.7%†	1.4%	1%	0.8%
Placebo	1.7%	1.5%	0.5%	0.9%
Decreased libido				
Avodart	3%†	0.7%	0.3%	0.3%
Placebo	1.4%	0.6%	0.2%	0.1%
Ejaculation disorder				
Avodart	1.4%†	0.5%	0.5%	0.1%
Placebo	0.5%	0.3%	0.1%	0%
Gynecomastia†				
Avodart	0.5%	0.8%†	1.1%†	0.6%†
Placebo	0.2%	0.3%	0.3%	0.1%

*considered by the investigator to have a reasonable possibility of being caused by the study medication; † includes breast enlargement and breast tenderness. †$P < 0.05$ *Avodart* vs placebo.

Effects on Vital Signs

Treatment with *Avodart* was not associated with clinically relevant alterations in blood pressure (BP) or heart rate (HR).(13,14,15) No significant changes from baseline systolic and diastolic BP measurements occurred in patients receiving *Avodart* (mean systolic BP change: –1.4 mmHg in each treatment group; mean diastolic BP change: –1.3 mmHg in the placebo group and –1.1 mmHg in patients who received *Avodart*). Similarly, no significant changes in baseline HR occurred (placebo group: mean increase of 0.5 beats/min, *Avodart*: mean increase of 1.0 beat/min).

Data from pre-clinical and clinical studies do not indicate any drug-related effects of *Avodart* on electrocardiogram (ECG) parameters, including the QTc interval.(71,72) *Avodart* 0.5 mg or 5 mg daily has been shown not to cause clinically or statistically significant changes in the QTc interval.(71)

Effects on Laboratory Tests

Changes in laboratory test values were consistent across the treatment groups. (66) No consistent patterns were noted when comparing the distribution of abnormal laboratory values. The rates of laboratory values that were outside threshold levels were similar between treated patients who received placebo or *Avodart*, 6% and 5%, respectively.

Liver function tests (LFT) were performed throughout the trials in all patients, but abnormal laboratory tests were not uniformly reported as adverse events by investigators. With this in mind, abnormal LFT values (specifically, alkaline phosphatase and alanine aminotransferase) were reported as drug-related adverse events during the monotherapy clinical trials at a rate of <1% of patients in each treatment group.

Effects on Prostate Specific Antigen (PSA)

The concentrations of PSA generally decrease as the prostate volume decreases in patients treated with *Avodart*.(13,14,15) (66) In approximately half of patients, a 20% decrease in the PSA concentration is seen within the first month of monotherapy with *Avodart*.(13,14,15) The median percent decrease in PSA concentration in clinical trials was 40% at 3 months, 47% at 6 months, 51% at 12 months, 54% at 18 months, and 55% at 24 months. The decrease is predictable over the entire range of PSA concentrations, although it may vary in individual patients. In addition, the decrease was comparable for patients treated with *Avodart* regardless of baseline prostate volume (<40 cc, ≥40 cc), age (<65, ≥65 years), race (Caucasian, non-Caucasian), and baseline PSA (<3 ng/mL, ≥3 ng/mL).

5.2 Open-Label Extension Phase of Pivotal Trials

The primary outcome variables of the open-label extension studies were safety (adverse events and laboratory safety parameters) and tolerability.[8] The secondary variables were AUA-SI score, PV, and Qmax. Data on AUR and BPH-related surgical events were also collected.

Demographic Characteristics

The age range of the patient population was 50 to 89 years (mean age: 66 years) and 92% of patients were Caucasian.[63,64,65] Table 10 provides the pooled baseline data for the subjects entering the 2-year open-label phase of the three major monotherapy trials with *Avodart*.

Table 10. Mean Baseline Characteristics of Patients Enrolled in the Open-Label Phase of Clinical Trials with *Avodart* [8]

Parameter Measured	Placebo/*Avodart* (P/A) n = 1152	*Avodart*/*Avodart* (A/A) n = 1188
AUA-SI units	16.9	16.6
Q_{max} (mL/sec)	10.7	10.2
Total Prostate Volume (cc)	53.9	56.1
Transition Zone Volume (cc)	26.9	28.6
Serum PSA (ng/mL)	3.9	4.1
AUA-SI = American Urological Association Symptom Index; Qmax = maximum urinary flow rate; PSA = prostate specific antigen		

Completion Rates

Over 4,300 male patients with BPH were randomly assigned to receive *Avodart* 0.5 mg daily or placebo in these trials. Among this group, 2,167 male patients received *Avodart* and 2,158 male patients received placebo for the first two years.[8] Of these, 1,510 and 1,441 patients, respectively, completed the first 2-year, double-blind phase of the trial. For the subsequent two years, 1,152 patients who had received placebo entered the open-label phase where all patients received *Avodart* (P/A group). Of these, 803 patients completed the entire 4-year study. Among the 1,188 patients who had received *Avodart* during the 2-year placebo-controlled phase of the study and enrolled in the open-label phase continuing to receive *Avodart* (A/A group), 864 patients completed the entire 4-year study.

In total, 1,667 patients completed the entire 4-year study. During the open-label phase, 29% of patients discontinued the study, mainly due to an adverse event (10% in P/A group and 9% in A/A group). Other common reasons for discontinuation included consent withdrawn (6% in both groups) and lack of efficacy (6% in P/A group and 4% in A/A).[63,64,65]

Efficacy Results

The efficacy results provided in Table 11 represent a pooled analysis from the three trials of *Avodart* from the beginning of the double-blind phase to the end of the open-label phase in men with BPH.[8,63,64,65] These data are presented as the percent change from baseline after the initial placebo run-in phase to year 4 for the intent-to-treat (ITT) population, including the 2-year double-blind phase, as well as the 2-year open-label phase.

Men who received *Avodart* 0.5 mg daily for all four years experienced sustained efficacy as evidenced by the following results compared to baseline: continued reductions in prostate volume (mean decrease of 27.3%), improvements in urinary symptoms (6.5 unit mean reduction in the AUA-SI score) and increased maximum urinary flow rates (Q_{max}, mean increase of 2.7 mL/sec).[8,63,64,65] Men who received *Avodart* at the initiation of the trial and continued through four years of treatment had consistently greater responses in AUA-SI scores, Q_{max}, and prostate volume than men treated with *Avodart* for only two years during the open-label phase. Incidence of acute urinary retention and rates of BPH-related surgery were significantly lower in patients receiving *Avodart* for all 4 years. The number of AUR events was higher during the first six months and tended to decrease over time.[63,64,65] The most common type of BPH-related surgery was transurethral resection (TURP).

Table 11. Efficacy Results from Extension Phase (4-Year Data) of Monotherapy Trials with *Avodart** **(8,63,64,65)**

Endpoints	Double-Blind Phase (Years 1-2)†		Open-Label Phase (Years 3-4)‡	
	Placebo (n = 2158)	***Avodart* (n = 2167)**	**Placebo/*Avodart* (n = 1152)**	***Avodart/Avodart* (n = 1188)**
AUA-SI(8)	-2.5 units	-4.4 units§	- 5.6 units‖	- 6.5 units¶
Total Prostate Volume (8)	+1.4 %	-26.0 %§	-21.7 %‖	- 27.3 %¶
Transition Zone Volume(63,64)	+ 10.4 %	- 21.7 %	- 14.2 %	- 20.0 %
Serum DHT(8)	+ 5.9 %	- 93.7 %	- 95.4 %	- 95.3 %
Serum Testosterone(8)	+2.2 %	+ 19.7 %	+ 20.7 %	+ 21.9 %
Maximum Urinary Flow Rate (Q_{max})(8)	+ 0.6 mL/sec	+ 2.2 mL/sec§	+ 1.9 mL/sec‖	+ 2.7 mL/sec#
BPH-Related Surgery(7,8)	4.1 %	2.2 %	4.5 %	2.6 %
Acute Urinary Retention (AUR)(7,8)	4.2 %	1.8 %	5.1 %	2.4 %

*Mean change from baseline after 2 years of double-blind therapy with placebo, followed by open-label *Avodart* for 2 years or 2 years of double-blind therapy with *Avodart* followed by open-label *Avodart*; †Results presented for double-blind phase at month 24; ‡Results presented for open-label phase at month 48; §$P<0.001$ vs. placebo; ‖$P<0.001$ vs. Month 24; ¶$P<0.001$ vs. Placebo/*Avodart*; #$P=0.042$ vs. Placebo/*Avodart*; AUA-SI = American Urological Association Symptom Index; DHT = dihydrotestosterone

Adverse Events

The overall incidence of drug-related adverse events during the 2 year, open-label extension phase was 12% for the P/A group and 8% for the A/A group.(63,64,65) The most common drug-related adverse events included impotence, decreased libido, ejaculation disorders, and gynecomastia (Table 12).(8) The exact mechanism for these events is unknown; but may be related to the androgenic effects of *Avodart*. The incidence of drug-related adverse events that led to withdrawal was less than 1% in the open-label phase.

Table 12. Summary of Drug-Related Adverse Events with an Incidence ≥ 1% in Either Treatment Group in Open-Label Extension Trials (ITT)(63,64,65)

Drug-Related Adverse Event	Placebo/*Avodart* N = 1152 n (%)	*Avodart*/*Avodart* N = 1188 n (%)
Impotence	36 (3%)	21 (2%)
Decreased libido	30 (3%)	6 (<1%)
Ejaculation Disorders	17 (1%)	4 (<1%)
Gynecomastia	23 (2%)	28 (2%)

ITT = intent-to-treat patient population

Reports of new onset sexual function adverse events were most frequently reported during the first six months of treatment among patients receiving *Avodart* for the entire 4-year period. With the exception of gynecomastia, the onset of new sexual adverse events decreased over time (Table 13).(8)

Table 13. Drug-Related Sexual Adverse Events Reported in > 1% of Patients during the 24-Month Open-Label Phase (Years 3 and 4)[8]

Adverse Event	Month 24 - 36		Month 36 - 48	
	P/A (n = 1152)	A/A (n = 1188)	P/A (n = 968)	A/A (n = 1041)
Impotence	2.8%	1.4%	0.4%	0.4%
Decreased libido	2.4%	0.4%	0.2%	0.1%
Ejaculation Disorders	1.2%	0.3%	0.3%	0.1%
Gynecomastia	1.3%	1.8%	0.9%	0.7%
P/A=placebo/*Avodart*; A/A=*Avodart/Avodart*				

6. CO-PRESCRIBED/CONCOMITANT THERAPIES

6.1 CombAT Trial

Study Design

Combination *Avodart* and Tamsulosin (CombAT) trial was a 4-year multicenter, randomized, double-blind, parallel-group study that evaluated whether combination therapy including *Avodart* and tamsulosin was more effective than either monotherapy alone for improvement of symptoms and long-term clinical outcomes of acute urinary retention (AUR) and prostate-related surgery.[10,73] Inclusion criteria included men aged ≥50 years of age with a clinical diagnosis of benign prostatic hyperplasia (BPH), an International Prostate Symptom Score (IPSS) ≥12 points, prostate volume (PV) ≥30 cc by transrectal ultrasonography (TRUS), total serum prostate specific antigen (PSA) 1.5-10 ng/mL, and urinary flow (Qmax) >5 and ≤15 mL/sec with a minimum voided volume ≥125 mL. Patients were randomized (N= 4,844) after a 4-week placebo run-in period to *Avodart* 0.5 mg, tamsulosin 0.4 mg, or the combination once daily for 4 years. A 2-year interim analysis was performed. Once the analysis of the 4-year data is complete, these results will be published.

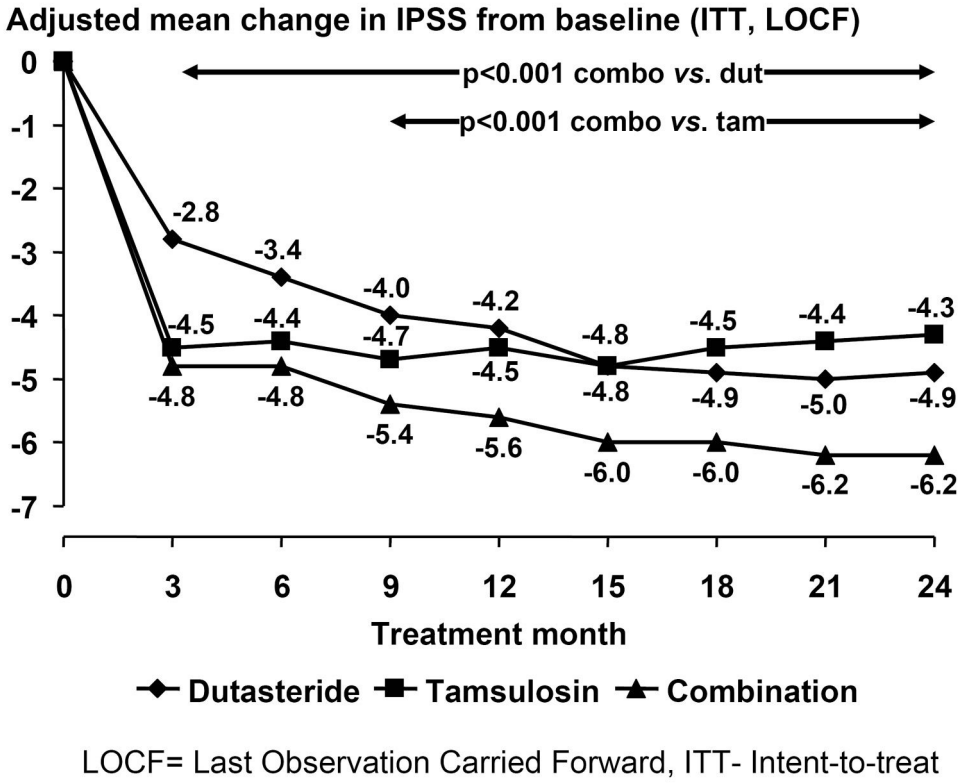
The primary endpoint at Year 2 was change from baseline in IPSS. The secondary endpoints included ≥ 3 point improvement from baseline IPSS, improvement of 3 mL/sec in Qmax, change from baseline in total PV and change from baseline in transition zone volume (TZV). Urinary symptoms were assessed every three months and peak urinary flow was assessed every six months.

Change from Baseline in IPSS (Primary Endpoint)

Baseline IPSS scores averaged 16.4 across the three treatment groups.[10] The reductions in symptom scores were significant for combination therapy versus *Avodart* from Month 3 and demonstrated continuous improvement to Month 24 (-6.2 vs, -4.9, $P < 0.001$). The reductions in symptom scores for the combination therapy versus tamsulosin were significant from Month 9 and demonstrated continuous improvement to Month 24 (-6.2 vs. -4.3, $P < 0.001$)(Figure 5).

The mean IPSS at Month 24 was 10.1 in patients receiving combination therapy, 11.4 in patients receiving *Avodart*, and 11.9 in the patients receiving tamsulosin.

Figure 5. Primary Endpoint: Mean Change from Baseline in IPSS[10]



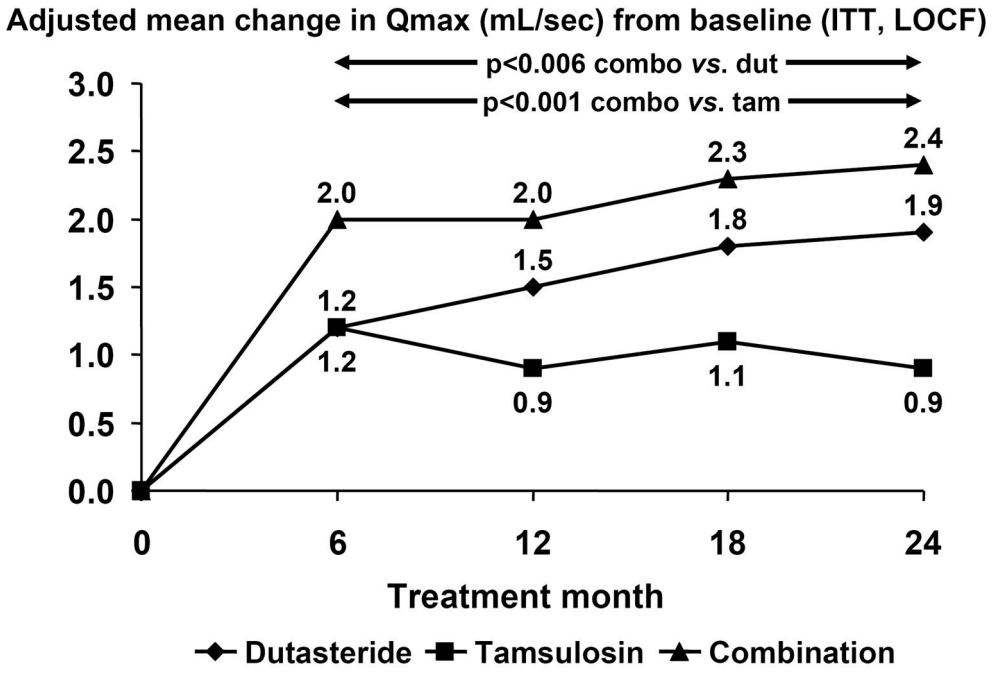
LOCF= Last Observation Carried Forward, ITT- Intent-to-treat

IPSS Responders and Qmax Responders

In the combination therapy group, 72% of men enrolled in the study experienced symptom improvement of ≥ 3 points from baseline at Month 24 compared to *Avodart* and tamsulosin, 65% and 62%, respectively.[10]

Baseline Qmax averaged 10.7 mL/sec across the three treatment groups. Increases from baseline in Qmax were significantly higher on combination therapy compared with each monotherapy from Month 6 to 24 (Figure 5). At Month 24 increases in Qmax from baseline were 2.4 mL/sec for combination therapy, 1.9 mL/sec for *Avodart*, and 0.9 mL/sec for tamsulosin.

Figure 6. Secondary Endpoint: Mean Change from Baseline in Qmax [10]

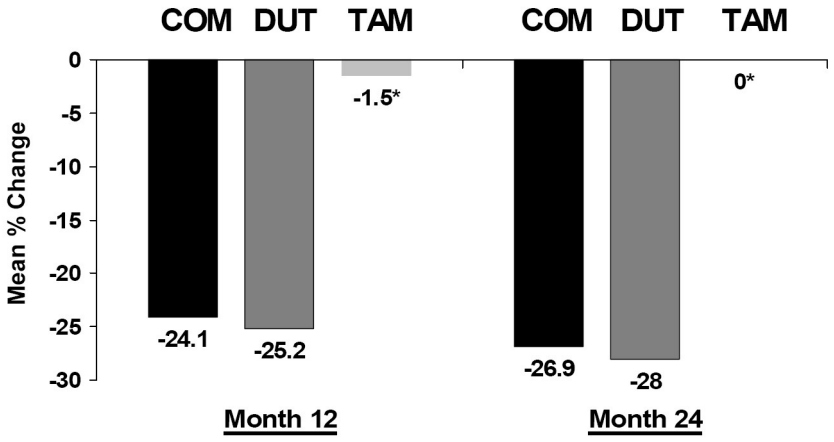


LOCF= Last Observation Carried Forward, ITT- Intent-to-treat

Change from Baseline in Prostate Volume

Baseline prostate volume (PV) averaged 55 cc.[10] At both Month 12 and 24, the adjusted mean percentage change from baseline in PV was significant for combination therapy versus tamsulosin. Neither Month 12 nor 24 showed significant differences in percentage change from baseline in PV between the combination therapy and *Avodart* (Figure 7).

Figure 7. Adjusted Mean Percentage Change from Baseline in Prostate Volume (LOCF, ITT Population)[10]



*p<0.001 Combo vs Tam

COM=*Avodart* and tamsulosin, DUT=*Avodart*, TAM=tamsulosin,
LOCF=Last Observation Carried Forward, ITT=Intent-to-treat

Change from Baseline in Transition Zone Volume

The transition zone volume (TZV) was determined in a subset of patients and was measured at month 12 and month 24.[74] Baseline values for TZV averaged 29.5 cc.[10] Reduction in TZV was significantly greater in the combination therapy group compared to the increases observed in the tamsulosin group ($P < 0.001$); however, there were no statistically significant reductions in TZV with combination therapy compared to *Avodart* at either time point.[10,74] See Table 14.

Table 14. Median Percent Change in Transition Zone Volume from Baseline in the CombAT Trial (At Visit)[74]

	***Avodart* 0.5 mg and tamsulosin 0.4 mg daily**	***Avodart* 0.5 mg daily**	**Tamsulosin 0.4 mg daily**
Month 12	-20.9%* n = 144	-22.7% n = 157	-2.8% n = 157
Month 24	-25.3%* n = 120	-30.8% n = 136	3.4% n = 131
*$P < 0.001$ vs tamsulosin			

Safety Analysis

In the Year 2 interim analysis of the Combination *Avodart* and Tamsulosin (CombAT) trial, the overall incidence of adverse events (AE) and serious adverse events were similar across the treatment groups.[10] The incidence of drug-related AEs was significantly higher in the combination therapy group compared with each monotherapy group (see Table 15). The discontinuation rate due to drug-related AEs was 5% for combination therapy and 3% for *Avodart* and tamsulosin as monotherapy.

Table 15. Drug-Related Adverse Events Occurring in ≥ 1% of Any Treatment Group[10]

Adverse Event	**Combination* n = 1610 (%)**	***Avodart* 0.5mg n = 1623 (%)**	**Tamsulosin 0.4mg n = 1611 (%)**
Erectile dysfunction	7.4	6	3.8
Retrograde ejaculation	4.2	0.6	1.1
Altered (decreased) libido	3.4	2.8	1.7
Ejaculation failure	2.4	0.5	0.8
Semen volume decreased	1.8	0.3	0.8
Loss of libido	1.7	1.3	0.9
Dizziness	1.6	0.7	1.7
Breast enlargement	1.4	1.8	0.8
Nipple pain	1.2	0.6	0.3
Breast tenderness	1	1	0.3
* *Avodart* 0.5mg and tamsulosin 0.4mg			

6.2 SMART Trial

Background on Drug-Interactions Between 5 Alpha-Reductase Inhibitors and Alpha-Blockers

Clinical drug interaction studies have shown no pharmacokinetic or pharmacodynamic interactions between *Avodart* and either tamsulosin or terazosin.[62] In a single sequence, cross-over study in healthy volunteers, the administration of tamsulosin or terazosin in combination with *Avodart* had no effect on the steady-state pharmacokinetics of either alpha-adrenergic blocker. Drug interaction studies between *Avodart* and doxazosin or alfuzosin have not been conducted.

CLINICAL DATA

SMART-1 Trial

The Symptom Management After Reducing Therapy (SMART-1) trial was a multicenter, double-blind, randomized trial designed to examine the effect of short-term (24-week) combination therapy with *Avodart* and tamsulosin, followed by withdrawal of tamsulosin or continuation of combination therapy in men with symptomatic BPH.(75) The secondary endpoint of SMART-1 was to investigate the tolerability of *Avodart* in combination with tamsulosin. Inclusion criteria included men being ≥45 years of age and having an International Prostate Symptom Score (IPSS) ≥ 12 (i.e., moderate to severe symptoms of BPH) and a prostate volume ≥ 30 cc, as determined by digital rectal examination (DRE). Patients were excluded if they had a prostate specific antigen (PSA) score < 1.5 ng/mL or > 10 ng/mL.

After a 4-week, single-blind, placebo run-in phase, patients were randomized to receive *Avodart* 0.5 mg and tamsulosin 0.4 mg daily for 24 weeks. At week 24, the double-blind phase began where patients either continued on combination therapy for 12 weeks (combination group, n = 164) or were switched to *Avodart* plus placebo (*Avodart* monotherapy, n = 163). The primary objective was to assess any difference at 30 weeks post-baseline in the proportion of subjects experiencing an improvement or no change in their urinary symptoms. This was assessed by response to the following question: "Over the past 2 weeks, on average have you felt better, worse, or the same, with respect to your urinary symptoms, than at your last visit?" The mean change in IPSS was a secondary endpoint of the trial. (75)

At week 30, 91% of patients treated with combination therapy and 77% of patients treated with *Avodart* monotherapy reported feeling better or the same with respect to urinary symptoms compared to week 24 (95% CI: -18%, -4%; $P = 0.001$) (see Figure 8). Among the patients who changed to *Avodart* monotherapy at week 24 with baseline IPSS < 20, 84% switched without any obvious deterioration in symptoms compared to 93% for those patients that remained on combination therapy. In the patients with severe baseline symptoms (IPSS ≥ 20) who had withdrawal of tamsulosin therapy at week 24, 42.5% reported a worsening of urinary symptoms compared with 14% in the combination group.Figure 9).(75)

Figure 8. Primary endpoint question at week 30 (IPSS)

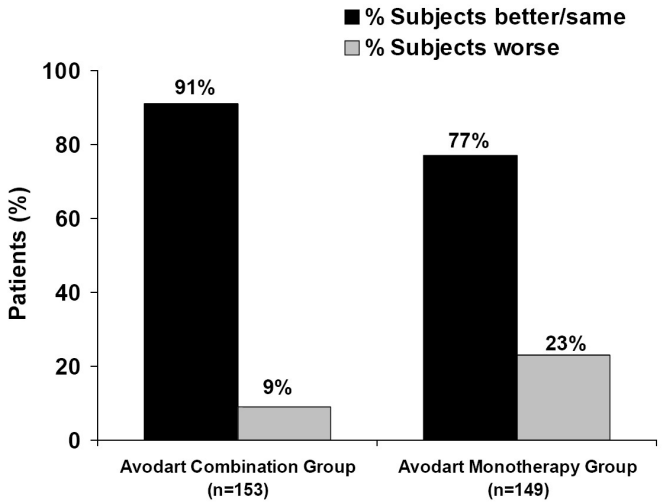
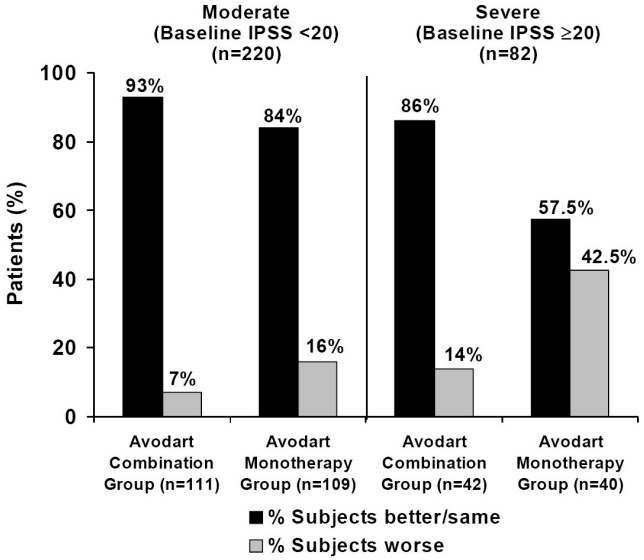


Figure 9. Primary endpoint question at week 30 (IPSS)



Results from the IPSS data correlated with those from the primary endpoint. During the first 24 weeks, the change in mean IPSS for patients on combination therapy was –5.3. After week 24, the change in mean IPSS scores were –0.4 (combination therapy) and +1.0 (monotherapy) at 30 weeks. At week 36, the change in mean IPSS scores for combination therapy was –0.5 and –1.1 for monotherapy.[75]

Overall, both regimens were well tolerated. Drug-related adverse events were reported in 25% of patients up to week 24. From weeks 24 to 36, 7% of patients treated with combination therapy and 3% of patients on monotherapy with *Avodart* reported an adverse event. Ejaculation disorders (7%) were the most frequently reported adverse events in the first 24 weeks of the study. There were generally no differences in the incidences of adverse events between the treatment groups between weeks 24 and 36 (following tamsulosin withdrawal).[75]

The authors concluded that SMART-1 defined a role for short-term alpha-blocker therapy (6 months), indicating that tamsulosin may be withdrawn in a majority of men (77%) initially treated with combination therapy. However, patients with more severe symptoms may benefit from longer term combination therapy. Because this study was designed to evaluate the effect of alpha-blocker discontinuation on existing combination therapy, the efficacy of the drug combination compared to either drug alone cannot be determined from this data. Results from the second phase of the trial revealed no excess of serious adverse events or discontinuations due to adverse events in the combination group versus the *Avodart* monotherapy group.[75]

7. OTHER STUDIED USES

7.1 Androgenetic Alopecia or Hair Loss in Males

BACKGROUND

Androgenetic alopecia (AGA) is also known as male pattern hair loss (MPHL). In AGA, naturally circulating androgens progressively transform large terminal scalp follicles to smaller, vellus ones, and result in visibly less dense scalp hair and eventually baldness.[76,77]

Testosterone is the major circulating androgen in the body, but must be converted to dihydrotestosterone (DHT) via the enzyme 5α-reductase in order to be active in the skin.[78] Studies have shown that men with 5α-reductase deficiency do not develop AGA.[78,79] Therefore, 5α-reductase inhibitors have been evaluated for the treatment of AGA due to their ability to inhibit the conversion of testosterone to DHT.[78,80] There

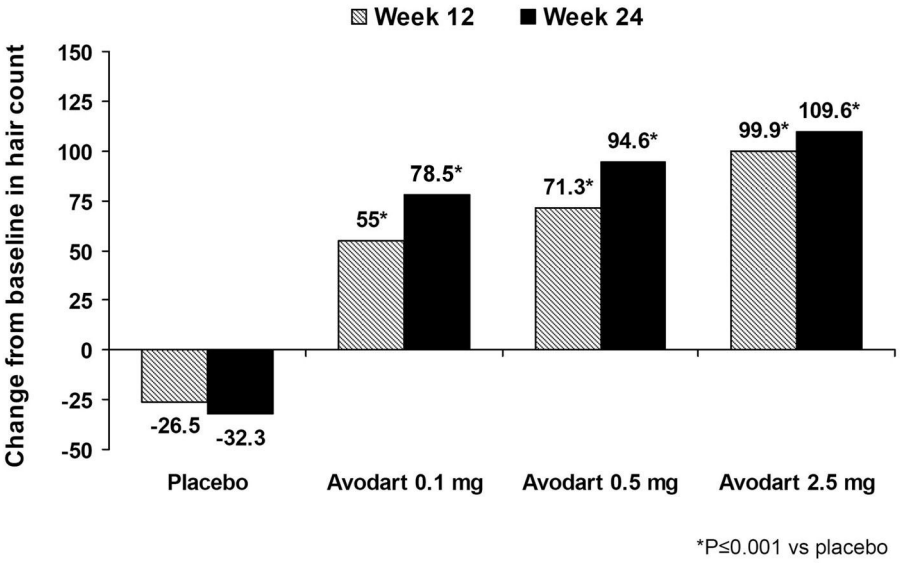
are two isoforms of 5α-reductase, type 1 and type 2. Type 2 is predominately located in human genital tissue. Type 1 is distributed throughout the body, and predominates in the skin and scalp.(78)

CLINICAL INFORMATION

A multicenter, double-blind, placebo-controlled study was conducted in 416 males with AGA (ages, 21 to 45 years; mean age, 36 years) to evaluate the dose-response relationship of repeated doses of *Avodart* 0.05 mg (n = 71), 0.1 mg (n = 72), 0.5 mg (n = 68), and 2.5 mg daily (n = 71) on hair count compared to placebo (n = 64) or finasteride 5 mg (n = 70) daily for 24 weeks.(81) Note that finasteride is approved for the treatment of AGA at a dose of 1 mg daily, but this strength was not commercially available at the time of study initiation. Patients were included in this study if they had mild-to-moderate MPHL defined as type IIIv, IV, or V Norwood-Hamilton patterns. The study had a screening evaluation, 24-week treatment period, and a follow-up visit for evaluation of hair count at 36 weeks. Hair regrowth was measured based on hair counts of the vertex region of the scalp using a macrophotographic technique. The primary efficacy parameter was the hair count in a 1-inch diameter circle, with a target area of 0.79 square inches, surrounding a tattoo. Mean baseline hair counts ranged from 902.1 to 1000.6 hairs per 1-inch target area and did not differ between groups.

After 24 weeks of treatment, mean hair counts decreased by 32.3 hairs in the placebo group and increased in active treatment groups. *Avodart* 0.1, 0.5, and 2.5 mg and finasteride were associated with significantly improved mean change in hair count from baseline at weeks 12 and 24 compared with placebo ($P \leq 0.001$) (Figure 10).

Figure 10. Mean Changes In Hair Counts Compared With Baseline After 12 And 24 Weeks Of Treatment With *Avodart* And Placebo (81)



The percentage of patients with ≥10% increase in hair counts was 0% for placebo; 17%, 38%, 48%, and 56% for *Avodart* 0.05 mg, 0.1 mg, 0.5 mg, and 2.5 mg, respectively; and 41% for finasteride.(81) Expert panel assessment of global photographs and investigators' global assessment were also significantly improved with *Avodart* compared with placebo.

Serum and scalp DHT concentrations were significantly suppressed and testosterone concentrations increased, in a dose-dependent manner, in patients receiving *Avodart* compared with placebo. Serum DHT suppression showed the greatest median effect at 24 weeks with *Avodart* 0.5 mg (92%) and 2.5 mg (96.4%). Scalp DHT concentrations decreased by 51% with *Avodart* 0.5 mg and 79% with *Avodart* 2.5 mg. Changes in scalp DHT concentrations were inversely correlated with change in hair count, panel assessments of the vertex, and investigators' assessment of the vertex (all $P \leq 0.001$).

There were no significant differences in total adverse events, serious adverse events, or withdrawals due to adverse events among any of the treatment groups, including placebo. The most commonly reported

adverse event was decreased libido, experienced by 9 patients (13%) receiving *Avodart* 2.5 mg; of these patients, 4 cases resolved while continuing *Avodart*, 2 resolved following discontinuation, and 1 continued following discontinuation and was considered unrelated to study drug. Two patients in each group receiving *Avodart* 0.05 mg, *Avodart*0.1 mg, and placebo; and 1 patient receiving *Avodart* 0.5 mg experienced decreased libido.

IN VITRO STUDY DATA

A study by Munster et al determined the effects of dutasteride and 17α- and 17β-estradiol on testosterone metabolism in human skin samples.[82] Human keratinocytes and fibroblasts from juvenile foreskin, occipital scalp skin, and dermal papilla cells were cultured and prepared from 3 female and 4 male donors. The cultures were incubated in either 17α-, or 17β-estradiol, or dutasteride to determine the inhibition of testosterone metabolism in these cells. After the extraction of androgens by thin layer chromatography, it was shown that dutasteride inhibited DHT synthesis. Since this was an *in vitro* study, these findings must be interpreted with caution.

8. COMPARATIVE DATA

8.1 Comparison of *Avodart* versus Finasteride in Patients with Benign Prostatic Hyperplasia

Clinical Information

No long-term clinical trials (≥ 2 years) have directly compared the safety and efficacy of *Avodart* and finasteride. Without such trials, conclusions regarding the relative efficacy and safety of one agent over the other cannot be made. The data from respective product local labels do not necessarily represent head-to-head comparative trials. However, short-term comparative data are discussed below.

Short Term Comparative Clinical Data

EPICS (Enlarged Prostate International Comparator Study) was a randomized, double-blind, active-controlled trial that compared 12 month therapies with *Avodart* and finasteride in 27 European countries. The study was conducted to fulfill European registration requirements. The primary objective of the study was to assess the change in baseline prostate volume. Secondary endpoints were change in American Urological Association Symptom Index (AUA-SI) score, peak urinary flow rate (Qmax), post-void residual volume (PVR), serum prostate specific antigen (PSA) and other safety and tolerability data. Patients with benign prostatic hyperplasia (BPH) were randomized to receive either *Avodart* 0.5 mg once daily (n = 813) or finasteride 5 mg once daily (n = 817) for 12 months. Of the patients randomized, 1,454 completed the 12-month double-blind phase (719 patients treated with *Avodart* and 735 patients treated with finasteride).[83]

Patients enrolled were males ≥ 50 years of age with a diagnosis of BPH (according to medical history and physical examination, including digital rectal exam), AUA-SI score ≥ 12, prostate volume ≥ 30 cc (as determined by transrectal ultrasound), urinary flow rate ≤ 15 mL/sec, and a minimum voided volume ≥ 125 mL. Patients were excluded if they had a post-void residual volume > 250mL or serum PSA < 1.5 ng/mL or > 10 ng/mL.[83]

At baseline, mean prostate volumes were 52.4 cc in the finasteride group (range: 21.47 - 155.04 cc) and 54.2 cc in patients treated with *Avodart* (range 25.61 - 197.39 cc). Baseline AUA-SI scores were similar for subjects of each treatment group, with a mean score at baseline of 16.5 in the finasteride group (range 1-35) and 16.7 in the treatment group that received *Avodart* (range 4-35). Mean Qmax values were 10.0 mL/sec in the finasteride treatment group (range 2.5-29.5 mL/sec) and 10.1 mL/sec in patients treated with *Avodart* (range 2.6-23.9 mL/sec).

For the intent-to treat patient population, prostate volume was reduced from baseline in patients treated with either *Avodart* or finasteride by month 12. The difference between the two agents was not statistically significant with regard to the primary or secondary endpoints of the study. *Avodart* produced numerically, but not significantly, greater improvements in symptoms and urinary flow rates compared with finasteride.[83] Results for primary and secondary endpoints are provided in Table 16.

Table 16. EPICS Primary and Secondary Efficacy Results in the ITT Patient Population (Adjusted Means – LOCF) [83]

	TPV (% change)	AUA-SI Score (change)	Qmax (mL/sec) (change)	PVR (% change)	PSA (% change)
Avodart 0.5 mg (n = 813)*	–26.3	–5.8	2	–22.1	–49.5
Finasteride 5 mg (n = 817)*	–26.7	–5.5	1.7	–14.9	–47.7
EPICS=Enlarged Prostate International Comparator Study; ITT=intent-to-treat patient population; LOCF=last observation carried forward; TPV=total prostate volume; AUA-SI=American Urological Association Symptom Index; Qmax=urinary flow rate; PVR=post-void residual volume; PSA=prostate specific antigen					

Although fewer drug-related sexual adverse events occurred in patients who received *Avodart* than finasteride, the overall rate of drug-related adverse events was similar between the two drugs. The most frequent drug-related adverse events were sexual in nature and are provided in Table 17.[83]

Table 17. Summary of Drug-Related Adverse Events after 1 year of Treatment with *Avodart* or Finasteride[83]

	Avodart 0.5 mg daily n = 813	Finasteride 5 mg daily n = 817
Any adverse event	17%	20%
Sexual adverse events & Gynecomastia	11%	14%
Impotence	7%	8%
Decreased libido	5%	6%
Ejaculation disorders	1%	1%
Gynecomastia	1%	1%

Few adverse events led to patient withdrawal from the study (5% of *Avodart* patients and 4% of finasteride-treated patients).[83] Thus, *Avodart* appeared to be as safe as finasteride for patients with BPH.

A 3-month prospective, non-randomized study was conducted to evaluate the onset of symptom relief with *Avodart* versus finasteride.[84] Men with symptomatic BPH were treated with *Avodart* (n=120) or finasteride (n=120) for 3 months. At baseline, no significant differences were noted among patients in terms of age or serum PSA levels. Patients were instructed not to expect any symptomatic benefit until at least 6 months. The AUA-SI was used to assess symptom scores at baseline and following 3 months of therapy.

Among patients who received *Avodart*, there were significantly greater reductions in AUA-SI scores compared with finasteride (Table 18). The estimated difference between the two treatment groups in patients demonstrating improvement was 20% (95% CI; 7.5%, 32.5%; $P < 0.0016$).

Table 18. Improvement in AUA-SI Score After 3 Months of Treatment with *Avodart* Compared to Finasteride[84]

	Avodart (n=120)	Finasteride (n=120)
No change	68 (57%)	92 (77%)
1 unit change	36 (30%)	22 (18%)
2 unit change	14 (12%)	5 (4%)
3 unit change	2 (2%)	1 (1%)

Serum DHT Reduction

A Phase II, dose-ranging trial with *Avodart* in patients with BPH (n = 392) and an enlarged prostate (≥ 30 cc as measured by transrectal ultrasound) directly compared various doses of *Avodart* with finasteride 5 mg daily in a double-blind, placebo-controlled study.[85] An additional follow-up phase for 4 months after patients had ended the double-blind phase was included. The study was not powered to detect clinical differences in symptoms between *Avodart* and finasteride. The mean reduction in baseline dihydrotestosterone (DHT) concentration in patients receiving *Avodart* 0.5 mg daily was greater and less variable than in patients receiving finasteride 5 mg daily (94.7 ± 3.3% and 70.8 ± 18.3%, respectively, $P < 0.001$). During the follow-up period (after study medication was stopped), mean DHT concentrations returned to within 20% of their baseline values at 16 weeks in patients receiving *Avodart*, compared with 4 weeks in those receiving finasteride.

Comparative Affinities of Avodart and Finasteride for the 5 Alpha-Reductase Isoenzymes

Finasteride is a competitive inhibitor of 5α-reductase that selectively inhibits the type 2 isoenzyme, with which it forms a stable enzyme complex.(86) This selective activity is attributed to a much lower affinity for the type 1 isoenzyme, and thus a slow rate of type 1 isoenzyme inhibition. In contrast, dutasteride is a competitive inhibitor of both forms of the isoenzyme, with 45-fold greater potency than finasteride against type 1 5α-reductase and 2.5-fold greater activity against type 2 5α-reductase. Thus, *Avodart* inhibits both type 1 and type 2 isoenzymes at clinically used doses.(62,86)

Whether clinical differences in the treatment of BPH occur between selective versus dual inhibitors of 5α-reductase is unknown.

9. OUTCOME AND ECONOMIC EVALUATION

Expected Outcomes of Therapy with *Avodart*

Pivotal trials have demonstrated clinical benefits in patients treated with *Avodart* 0.5 mg daily over placebo. The primary efficacy endpoint in these three large double-blind, placebo controlled clinical trials was the incidence of acute urinary retention (AUR). Over the 24-month period of the trials *Avodart* was associated with a 57% reduction in the risk of AUR compared with placebo ($P < 0.001$). (6) Therapy with *Avodart* was also associated with improvements in a number of secondary endpoints, including: (6)

- 48% reduction in the risk of BPH-related surgical intervention compared with placebo ($P < 0.001$).
- Improvement in symptoms, as measured by the American Urological Association Symptom Index (AUA-SI) score (mean decrease from baseline in AUA-SI score of –3.8 units for *Avodart* versus –1.7 units for placebo, $P < 0.001$).
- Reductions in mean prostate volume (PV) of –24.7% (adjusted for placebo) and a median reduction from baseline in dihydrotestosterone (DHT) concentration of 93%. Evidence also demonstrated a significant increase in urinary flow rate over the 2-year controlled trials.
- These endpoints were maintained or improved upon in the subsequent 2 year open-label extensions of these trials out to a total of 4 years.

Quality of Life and Other Humanistic Measures in the pivotal trials

BPH is primarily a quality of life disease. The consequences of BPH symptoms can affect physical, social, and psychological well being.(11) BPH can also significantly impact functional health by interfering with activities of daily living. The degree to which BPH symptoms affect quality of life and functional health is important to assess, since these factors may directly impact a patient's motivation to seek treatment.

The following humanistic assessments were used in the phase 2 and 3 clinical trials for Avodart (Table 19).

Table 19. Summary of Humanistic Assessments Included in Avodart Clinical Trials(12,13,14,15,87,88,89,90)

Instrument	Number of Items	Number of Scales	Response Options: Numeric Coding and Verbal Labels	Maximum Score	Positive Change
BII	4	1	0-3: none of the time- a lot/all of the time	12	Decrease
SPI	7	1	0-4: no problem-big problem	28	Decrease
BSIA	7	1	0-4: none of the time-all of the time (recorded as 0-4 to match other studies, standardized form is 1 to 5.)	28	Decrease
SFI*	11	5	N/A, depends on scale	N/A	Increase

AUA-SI = American Urological Association Symptom Index; BII = BPH Impact Index; SPI = Symptom Problem Index; BSIA = BPH Specific Interference with Activities; BPWB = BPH Psychological Well-being; MOS-Sleep = Medical Outcomes Study Sleep scale; * PASFI = Problem Assessment scale within the Sexual Function Inventory group of scales; N/A = not applicable.

Instrument	Number of Items	Number of Scales	Response Options: Numeric Coding and Verbal Labels	Maximum Score	Positive Change
BPWB	5	1	1-5: not at all-almost always.	25	Decrease
BSLA	3	1	1-6: none of the time to all of the time	18	Decrease
MOS-Sleep	6	5	1-6: all of the time-none of the time	36	Decrease
AUA-SI = American Urological Association Symptom Index; BII = BPH Impact Index; SPI = Symptom Problem Index; BSIA = BPH Specific Interference with Activities; BPWB = BPH Psychological Well-being; MOS-Sleep = Medical Outcomes Study Sleep scale; * PASFI = Problem Assessment scale within the Sexual Function Inventory group of scales; N/A = not applicable.					

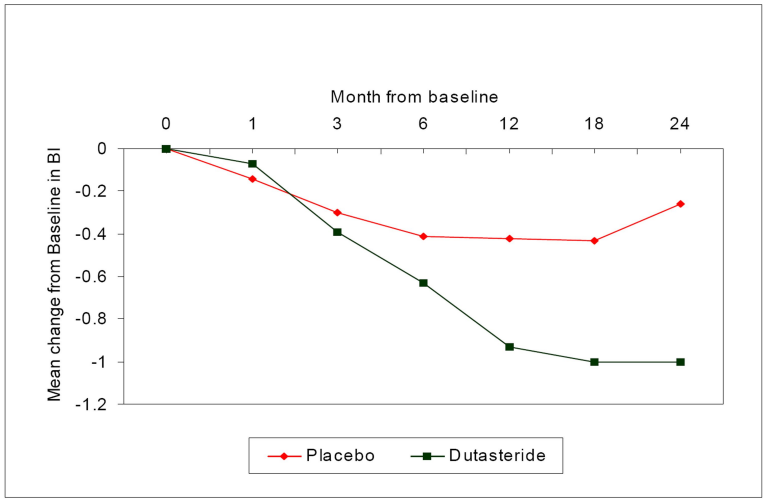
BPH Impact Index (BII)

The BII, administered at baseline and months 1, 3, 6, 12, 18, and 24, is a four-item instrument that evaluates the extent to which symptoms affect the patient's health status. It measures physical discomfort, activity restriction, bother, and worry associated with lower urinary tract symptoms. The BII is scored such that a decrease in score demonstrates an improvement in BPH-specific health status. A decrease in BII of –0.5 correlates with patient perceptions of improvement in symptoms and thus signifies a clinically significant difference.[12]

Avodart significantly improved patient health status compared with placebo ($P < 0.001$) as measured by reductions in the BII beginning at Month 12 in studies ARIA3001 and ARIB 3003 ($P < 0.001$).[13,15] and beginning at month 6 in ARIA3002 ($P = 0.014$).[14] For all three studies, these improvements were sustained through Month 24. (SeeFigure 11)

A clinically significant improvement was demonstrated for *Avodart* treated patients from month 6 in the pooled analysis with a change from baseline of –0.63 at month 6, increasing to –1.0 at month 24. BII scores continued to decrease (improvement in health status) for up to 18 months, and remained at –1.0 for the rest of the study for *Avodart* patients. In contrast, a clinically relevant improvement in health status was not achieved in the placebo group and placebo-treated patients showed little improvement from baseline from month 6 to month 18, deteriorating from months 18 to 24.[89]

Figure 11. Phase 3 pooled data: BII change from baseline, with a negative change reflecting improvement from baseline



When examining the subgroup of patients with baseline prostate volumes < 40 cc or ≥ 40 cc, significant improvement versus placebo ($P < 0.001$) was noted in BII scores for patients treated with *Avodart* who had larger prostates beginning at Month 12 and continuing through Month 24. For patients treated with *Avodart* with baseline prostate volumes < 40 cc, some improvements were noted at Months 18 and 24 in

ARIA3001 and at Month 24 in ARIB3003.[13,15] However, the interpretation of these results is restricted as defined by the multiplicity rules established for these protocols. In ARIA3002, beginning at month 6 and continuing through month 24, patients with prostate volumes ≥ 40 cc had significantly greater improvements in BII relative to placebo ($P \leq 0.002$). However, no statistically significant differences between treatment groups were found in ARIA3002 for patients with prostates < 40 cc. [14]

Symptom Problem Index (SPI)

The Symptom Problem Index (SPI), a companion measure to the AUA-SI, was chosen to assess symptom bother at baseline and months 12 and 24 only. [91]

Study protocol limitations allowed interpretation of SPI in studies ARIA3002 and ARIB3003. The mean baseline SPI values across treatment groups and protocols were comparable, ranging from 11.6 to 11.8 for the placebo treatment group and 11.6 to 12 for the *Avodart* treatment group. Using last observation carried forward (LOCF) analysis, significant improvements from baseline SPI in patients treated with *Avodart* relative to placebo were also comparable at months 12 and 24, with adjusted mean treatment differences ranging from –1.0 ($P = 0.002$)[14] to –1.1 ($P < 0.001$)[15] at 12 months and –1.7 to –1.8 at 24 months ($P < 0.001$). [14,15] Interpretation of treatment differences with regard to the SPI was restricted in study ARIA3001 due to the rules of multiplicity established for this study.[13]

When examining the subgroup of patients stratified by baseline prostate volume ≥ 40 cc significant improvements versus placebo were noted from baseline SPI in both studies ARIA3002 ($P < 0.001$) and ARIB3003 ($P \leq 0.003$). Significant improvement was not achieved for patients treated with *Avodart* who had baseline prostate volumes < 40 cc.[14,15]

BPH-Specific Interference with Activities (BSIA)

The disruption of daily activities by BPH was evaluated using the BSIA questionnaire at baseline and at treatment months 1, 3, 6, 12, 18, and 24. The BSIA asks patients to rate the frequency with which urinary symptoms interfere with activities, including such activities as sports and getting a sufficient amount of sleep. [15]

Baseline mean BSIA scores were comparable across treatment groups and protocols, ranging from 8.5 to 8.8. A significantly greater reduction in interference with activities was seen in patients who received *Avodart* relative to placebo in studies ARIA3002 (adjusted mean difference at month 24, –0.9; $P = 0.001$) and ARIB3003 (adjusted mean difference at month 24, –1.2; $P < 0.001$). [14,15] Although significant differences were noted in ARIA 3001 (at months 1 and 24), the interpretation of these treatment differences was again restricted due to the rules of multiplicity established in the study protocol. [13]

In ARIA3002 beginning at 12 months and continuing through 24 months, patients with prostate volumes ≥ 40 cc who were receiving *Avodart* experienced a significant reduction in BSIA relative to placebo ($P \leq 0.005$). However, no differences between treatment groups were seen in patients with prostate volumes < 40 cc. [15] In ARIB3003 patients with prostate volumes ≥ 40 cc who were receiving *Avodart* experienced a significant reduction in BSIA relative to placebo at month 24 ($P \leq 0.001$). For patients with prostate volumes < 40 cc a statistically significant reduction in BSIA was observed beginning at month 12 and continuing through month 24; however, these statistics have restricted interpretation due to the rules of multiplicity established for this study. [14]

Combined Symptom Problem Index and BPH Specific Interference with Activities

In order to control for the number of statistical tests that were performed on the SPI and BSIA, the final study reports implemented an algorithm to adjust for multiplicity. Change from baseline at Month 12 was compared across the SPI and BSIA in terms of their composite ranking. Based on these summed ranks, results for patients treated with *Avodart* were not significantly different from results reported for the placebo group in ARIA3001. However, significant differences were noted between *Avodart* and placebo groups in both studies ARIA3002 and ARIB3003 ($P = 0.002$). Given the mixed results, the interpretation of Study ARIA3001 data is limited with regard to SPI and BSIA measures.[13,14,15]

Problem Assessment Scale of the Sexual Function Inventory (PASFI)

The Problem Assessment scale is one of five scales in the Sexual Function Inventory. It consists of three items that evaluate the extent to which the subject has perceived as problematic the following: 1) lack of

sex drive; 2) ability to obtain and maintain erections; and 3) ejaculation. The three items are summed to yield a single score. The developers of the Sexual Function Inventory endorse use of this scale as a stand-alone questionnaire. They state that the scale provides a psychometrically sound index of how problematic respondents find their sexual status. [15]

At baseline, the mean PASFI scores in both *Avodart* and placebo treatment groups were 6.4 to 6.9. Mean change from baseline PASFI was examined at month 12 using a LOCF analysis. At Month 12, the adjusted mean score in patients treated with *Avodart* decreased by 1.0 (ARIA3002; $P < 0.001$)[15] to 1.1 (ARIA3001; $P = 0.009$)[13] , while the score for the placebo group remained unchanged or decreased by 0.6 units, respectively. This reduction in PASFI score indicated reduced sexual functioning in the patients who received *Avodart*.

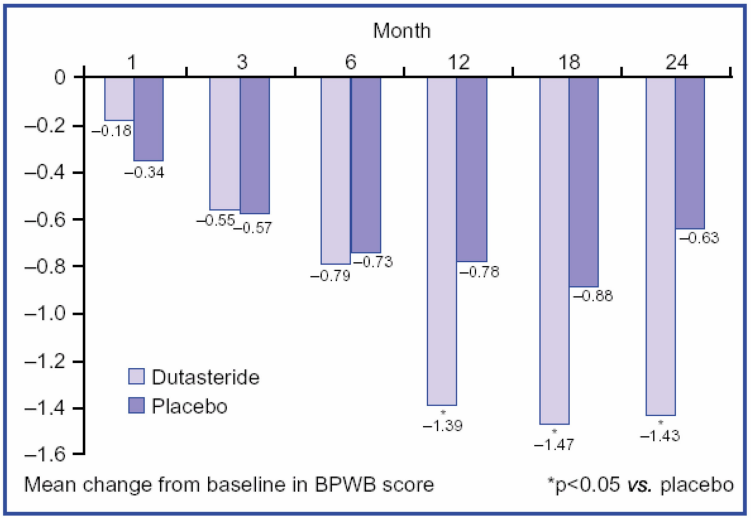
In ARIA3001 patients who had larger baseline prostate volumes (≥ 40 cc) who were treated with *Avodart* had a significantly worsened PASFI ($P = 0.03$) relative to placebo (LOCF), whereas in the At Visit analysis there was no significant difference between the groups. There was also no difference relative to placebo in patients receiving *Avodart* who had smaller baseline prostate volumes (< 40 cc) in this study. [13] However, in ARIA3002 sexual functioning in patients treated with *Avodart* was worsened in both LOCF and At Visit analyses in men with baseline prostate volumes ≥ 40 cc. However, no significant reduction or worsening in the PASFI was noted in *Avodart* patients relative to placebo when baseline prostate volume was < 40 cc. [15]

BPH Psychological Well-Being (BPWB) Questionnaire

The BPWB has five items, evaluating psychological impact of urological problems. Questions assess the impact of urinary problems on embarrassment, frustration, feeling down, worry, and a wish for improvement.[15,88] The overall score ranges from 5-25, with a positive effect being demonstrated by a decrease in score. The BPWB was administered in *Avodart* study ARIA3002 at baseline and months 1, 3, 6, 12, 18 and 24. [88]

At months 12, 18 and 24, the group of patients who received *Avodart* demonstrated a statistically significant improvement from baseline in mean BPWB total score, which was approximately twice the reduction compared to the placebo group.[88] These results are depicted in Figure 12.

Figure 12. Mean change from baseline in BPH Psychological Well-Being (BPWB) score at months 1-24



BPH Lifestyle Adaptations (BLSA) Questionnaire

The BPH-Specific Lifestyle Adaptations (BLSA) questionnaire was developed to evaluate the degree of lifestyle adaptation behaviors used to accommodate worsening symptoms of BPH. The questionnaire was used in two of the three pivotal, double-blind, placebo controlled, clinical trials with *Avodart*. Subjects were asked to select 3 out of 19 possible lifestyle adaptations and rate their frequencies on a scale of one to six (ranging from none of the time to all of the time). The questionnaire was administered at baseline, 12, and 24 months. Among enrolled patients after 24 months of treatment with either *Avodart* or placebo,

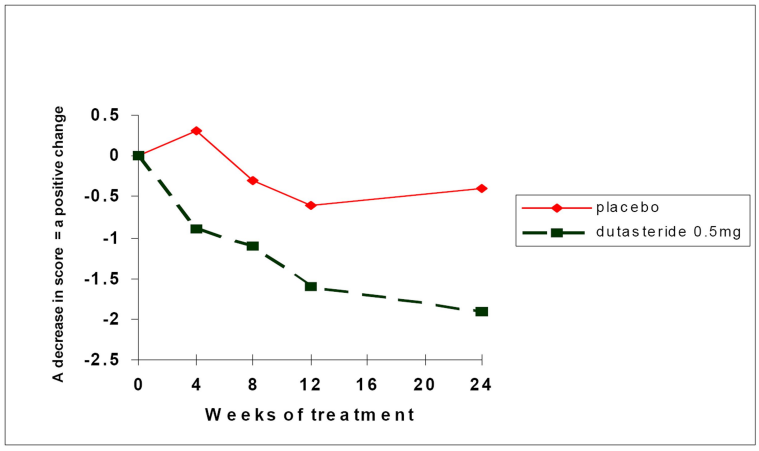
2430 patients reported at least one lifestyle adaptation at baseline. Treatment effects in favor of *Avodart* on 11 of 19 adaptations were recorded. The five most frequent adaptations with corresponding levels of significance favoring *Avodart* included: urinating before leaving home, chosen by 67% of patients ($P < 0.001$), trying not to drink as much (37% of patients, $P = 0.002$), always being aware of toilet locations (26% of patients, $P = 0.042$), using the restroom when available regardless of the need to go (26% of patients, $P < 0.001$), and urinating before beginning an activity (18% of patients, $P = 0.003$). In this study, relative to placebo *Avodart* significantly reduced the frequencies of the most commonly selected lifestyle adaptations on the BLSA. (90)

Medical Outcomes Study (MOS)-Sleep scale

The six-item version of the MOS-Sleep scale was administered in ARIA2001, a Phase II study, to evaluate the impact of urinary symptoms and their treatment on sleep quality. The MOS-Sleep Scale is a generic scale, therefore not all items are relevant to BPH. It contains multiple scales that can be scored and reported individually, and it is widely recognized as valid. Specifically, the MOS-Sleep scale measures five aspects of sleep quality: maintenance, overall sleep adequacy, daytime somnolence, sleep disturbance-initiation, and sleep-related respiratory problems. The overall score ranges from 0-36, with a positive effect being demonstrated by a decrease in score. The MOS-Sleep Scale was administered at baseline and weeks 4, 8, 12, and 24. (87)

At Week 24 (end of treatment), significant improvement in total score ($P < 0.05$) was reported in the *Avodart* group (adjusted mean change from baseline of –1.9) versus placebo (adjusted mean change from baseline of –0.4) (LOCF). Comparable results were noted when results were examined using an "At Visit" approach (see Figure 13).(87)

Figure 13. Phase II data: Adjusted mean change from baseline in MOS-Sleep score



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